ALVEOLAR AND ARTERIAL OXYGEN TENSIONS AND THE SIGNIFICANCE OF THE ALVEOLAR–ARTERIAL OXYGEN TENSION DIFFERENCE IN NORMAL MEN [1]

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We have had two objectives in determining alveolar and arterial oxygen tensions. It was hoped that they might be sensitive criteria for the normality of pulmonary oxygen transfer in health and disease. Secondly, a study of these oxygen tension values together with other respiratory measurements might further elucidate the process by which pulmonary artery blood becomes oxygenated as it perfuses the lung.

The purposes of this paper are: 1. To examine the validity and accuracy of the methods by which alveolar P_{O_2} is determined, the technique for estimating arterial P_{O_2} and P_{CO_2} having been critically discussed elsewhere (1). 2. To present the data from which the alveolar-arterial oxygen tension difference has been calculated in a group of normal men breathing atmospheric air. 3. To discuss the significance of this difference in the resting and exercise state.

The Validity and Accuracy of the Method for Calculating Alveolar P_{O_2}

The gas within the lungs is continuously fluctuating in composition and is not uniformly distributed (2, 3). For this reason and others of a technical nature (4, 5), direct sampling of alveolar gas, especially during exercise and in pathological subjects, will not disclose the true values of alveolar P_{O_2} and P_{CO_2}. An alveolar P_{O_2} may be calculated by means of the Bohr relation (6) and alveolar equations based on it (7, 8) provided that certain requirements are satisfied.

The Bohr relation can be used to calculate an alveolar P_{O_2} when the alveolar P_{CO_2} and the R.Q. of expired gas are known if one accepts as correct that "the R.Q. of expired and alveolar air are the same" (9). The R. Q. of expired gas can be accurately measured but if one wishes to calculate an alveolar P_{O_2} it is still necessary to know the alveolar P_{CO_2} during the period that the expired gas is collected. Rossier and Blickenstorfer (10) and Riley, Lilienthal, Proemmel, and Franke (11) have suggested that if one assumes that CO_2 equilibrium is attained between pulmonary capillary blood and alveolar gas one can substitute the directly measured arterial P_{CO_2} for alveolar P_{CO_2}, thus providing the remaining necessary term for calculating an alveolar P_{O_2}. Leaving the matter of whether or not the above equilibrium is always attained for later discussion, can one accept without reservation the hypothesis that the arterial P_{CO_2} measured during any one period is truly representative of the P_{CO_2} of the alveolar gas that contributed to the expired gas collected during the same period?

It is clear that this hypothesis is acceptable only when the ratio of the volumes of CO_2 and O_2 exchanged between pulmonary blood and alveolar gas and simultaneously between alveolar and expired gas is the same. In other words, when the R.Q. of the pulmonary blood phase, alveolar gas phase and expired gas phase are identical. Riley and Cournand (7) have stated "that the blood R.Q., the alveolar R. Q., and the expired air R.Q. are identical" when a "steady state" is attained. Since the calculation of an alveolar P_{O_2} requires that these R.Q.'s be equal, it is pertinent to examine the direct evidence bearing on the satisfaction of this requirement under actual conditions of measurement and to disclose those circumstances under which the requirement may be unfulfilled.

The CO_2–O_2 exchange ratio, when determined by analysis of expired gas collected over a sufficiently long period, represents the respiratory quotient of the body as a whole. When, however, expired gas is collected for brief periods, it is desirable to designate this ratio as R to indicate that

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TABLE I

Typical spontaneous variations of the breathing pattern and gas exchange observed in normal subjects breathing air at rest and during exercise

Exp. No. 1*	Minutes.....	1	2	3	4	5	6	7	8	9	10
Resting	MV	5.68	6.27	6.74	5.09	7.81	7.44	5.20	6.18	6.63	5.68
	O_2 Uptake	.213	.237	.226	.198	.258	.232	.192	.234	.226	.213
	R_E	.87	.84	.90	.79	.92	.91	.73	.74	.77	.76
Exp. No. 2	Collection time in sec.....	75	70	74	68	74	72	79	80	80	73
Resting	MV	6.98	6.48	6.50	6.68	7.28	7.08	6.65	6.45	6.38	6.80
	O_2 Uptake	.276	.250	.230	.228	.225	.234	.226	.234	.234	.250
	R_E	.80	.79	.81	.79	.83	.83	.80	.76	.80	.77
Exp. No. 3	Collection time in sec.....	143		134		129		130		131	
Resting	MV	5.20		5.13		5.11		4.96		5.53	
	O_2 Uptake	.219		.180		.175		.183		.218	
	R_E	.84		.84		.89		.77		.80	
Exp. No. 4	Minutes.....	1 and 2		3 and 4		5 and 6		7 and 8		9 and 10	
Exercise	MV	36.5		56.6		62.0		67.8		68.0	
	O_2 Uptake	1.795		2.350		2.520		2.595		2.495	
	R_E	.78		.99		.98		.99		.95	
Exp. No. 5	Minutes.....	4 and 5		9 and 10		14 and 15		19 and 20			
Exercise	MV	53.5		55.9		56.8		56.9			
	O_2 Uptake	2.050		2.060		2.045		2.030			
	R_E	.95		.94		.94		.93			

* *Exp. No. 1.* Moderately well-trained laboratory worker, two hours after breakfast, recumbent 25 minutes before ten successive one-minute expired air samples were collected with no loss of expired air between samples. Douglas bags rinsed with room air before experiment. Valves turned at the minute regardless of phase of respiration.

Exp. No. 2. Highly trained subject under the same conditions. Valves turned during inspiration after each 12 breaths.

Exp. No. 3. As in Exp. No. 2, but the valves were turned during inspiration after each 24 breaths.

Exp. No. 4. Normal subject, post-absorptive, walking at 3.5 mph., and on a 10 per cent grade on motor-driven treadmill. Successive two-minute collections made from the start of exercise.

Exp. No. 5. Normal subject, post-absorptive state, walking at 3.5 mph., on an 8 per cent grade. Two minute collections made at intervals as indicated.

it may not faithfully reflect overall body metabolism. This is the case, for example, during transient periods of hyperventilation. For purposes of this discussion, the CO_2–O_2 exchange ratio will be designated as R_E or R_B according to whether this ratio is calculated from analyses of inspired and expired gas, or from analyses of blood samples from the pulmonary and systemic arteries. R_A will designate the ratio of CO_2 and O_2 exchange between alveolar gas and pulmonary capillary blood.

In Table I are presented data on normal subjects who were accustomed to breathing through a mouthpiece which was part of the open circuit routinely used in this laboratory. In these subjects, every effort was made to allow them to reach a steady state with respect to breathing pattern, O_2 uptake, and R.Q. It is evident that at rest, and to a lesser extent during 10 to 20 minutes of exercise, there are fluctuations in R_E and O_2 uptake which cannot be accounted for on the basis of errors in Haldane analysis. The cause of these fluctuations is not immediately apparent but they bear on the concept of the steady state.

Cournand (12) has reported that R_E determined over a one to two minute period from analyses of expired gas does not always agree with R_B determined from analyses of the concurrently obtained mixed venous and systemic arterial blood of resting subjects. Occasionally, similar discrepancies between R_E and R_B have been observed in this laboratory in studies (13) carried out on anesthetized dogs even though the collec-

tions of gas and blood were made simultaneously over a period of several minutes. The influence of analytical errors in blood and gas analysis on the calculated values for R_E and R_B may explain such discrepancies in some instances. Consideration of other factors which might explain these discrepancies is of interest, however, in regard to the practical application of the Bohr relation for calculating alveolar P_{O_2}.

During changes in tidal volume, respiratory rate and functional residual capacity, the composition of expired gas varies in a complex fashion which is not entirely determined by CO_2 and O_2 exchange between blood and alveolar gas. With brief periods of hyperventilation, for example, the Haldane-Priestley alveolar P_{CO_2} drops 10 to 20 mm. Hg (14) and the CO_2 output measured from expired gas increases abruptly with very little change in O_2 uptake. If any CO_2 entering the expired gas cannot be accounted for by loss of CO_2 from the blood, R_E will be greater than R_B during the period of gas collection. Dubois, Fenn, and Britt (15) have estimated that lungs from which blood has been removed can take up (and therefore unload) about 0.23 cc. of CO_2 per 100 Gm. of lung tissue per mm. of change in CO_2 tension. Since CO_2 diffuses through body tissues quite rapidly, it is possible that a drop of 10 mm. Hg in alveolar P_{CO_2} could result in the excretion of 23 cc. of CO_2 from a kilogram of lung tissue.

When the functional residual capacity decreases, as it may during a brief period of observation, a higher concentration of CO_2 is found in the expired gas. The R_E will show no change as a result of such a change in functional residual capacity when the distribution of alveolar gas is uniform; however, when alveolar gas composition varies in different parts of the lung, a change in functional residual capacity may produce a change in R_E without there being a simultaneous change in R_A.

If R_E is as much as 0.04 unit greater than R_A during a short period of expired gas and arterial blood collection, the calculated alveolar P_{O_2} works out to be about 2 mm. too high. Since many patients tend to hyperventilate when breathing through a mouthpiece and since even in the trained normal subjects of Table I minute to minute R_E variations of 0.04 unit frequently occur, it is evident that the calculated alveolar P_{O_2} must be interpreted with due regard to the conditions required for its valid calculation.

There remains to be considered the assumption of Rossier and Blickenstorfer (10) and Riley, Lilienthal, Proemmel, and Franke (11) that equilibrium with respect to CO_2 is attained between alveolar gas and pulmonary capillary blood. There is little doubt that this assumption is justified when it is made with respect to normal animals and man at rest for it has been repeatedly shown (9, 16,17) that when alveolar gas is properly sampled its CO_2 tension is equal to that in arterial blood. Proof is needed, however, that this assumption is valid during the greater output of CO_2 that accompanies exercise.

Riley, Lilienthal, Proemmel, and Franke (11) using the Boothby modification of the Haldane-Priestley technique and other investigators (18) using an "end tidal" sampling device (19) found that the P_{CO_2} of directly sampled alveolar gas averaged 12.7 and 1.8 mm. Hg higher than the P_{CO_2} of simultaneously sampled arterial blood in normal subjects during exercise. Data obtained by us on normal men during exercise, using the Muller trap as modified by Henderson and Haggard (20), are presented in Table II. We found the average "alveolar P_{CO_2}" obtained thus to be 2.3 mm. Hg higher than that of arterial blood simultaneously sampled. That the difference observed by other investigators (18) and by us is so much less than that reported by Riley is obviously in a large measure accounted for by the methods used to obtain the "alveolar" sample. The theoretical analysis by Dubois (21) of the probable cyclic changes in alveolar P_{CO_2} emphasizes the necessity for cir-

TABLE II

The mean of measurements of P_{CO_2}, P_{O_2} and R of end-tidal samples compared with the mean of values in arterial blood, alveolar gas (calculated) and expired gas—The data were obtained during exercise in 30 of the normal subjects of Table IV

	P_{CO_2}	P_{O_2}	R
	mm. Hg	*mm. Hg*	
End-tidal	40.1	98.6	.928
Arterial	37.8		
Calculated alveolar		102.5	
Expired			.972
Mean of individual differences	2.3	3.9	.044
S.E. of mean of individual differences	.73	.91	.007

cumspection in the interpretation of data obtained by the direct sampling of alveolar gas.

If the diffusion theory of alveolar gas exchange is accepted, the P_{CO_2} of gas to which pulmonary blood is exposed cannot be higher than the P_{CO_2} of blood flowing from the alveolar capillaries. Roughton's work (22) indicates that alveolar capillary blood does not decrease in CO_2 tension as it flows to the peripheral arteries and hence it is unlikely that arterial P_{CO_2} is ever lower than that of the alveolar spaces. Data available by direct sampling show the alveolar P_{CO_2} to be consistently higher than that of arterial and presumably capillary blood. The discrepancy in this direction is understandable on the basis of inadequate methods for obtaining a true sample of gas from the alveoli and since no one has demonstrated discrepancies of opposite sign in normal persons, the data can be taken to support the assumption that the arterial P_{CO_2} and alveolar P_{CO_2} are virtually equal during exercise as well as at rest in normal subjects.

The experimental data of Table II nicely demonstrate the type of error that is produced by a direct sampling method for measuring end-tidal gas concentrations during exercise. The end-tidal P_{O_2} was 3.9 mm. Hg less than the calculated alveolar P_{O_2}. Of this difference, 2.3 mm. Hg can be accounted for by the fact that the end-tidal P_{CO_2} was 2.3 mm. Hg less than in arterial blood. The remaining 1.6 mm. Hg can be accounted for by the fact that the end-tidal R is significantly less than the R of mixed expired gas as would be expected from the work of Stacy and Kydd (23). Considering the blood dissociation curves and diffusion characteristics of O_2 and CO_2, it is probable that toward the end of an expiration the rate of O_2 uptake and therefore loss of O_2 from alveolar gas remains quite rapid even though the output of CO_2 from the blood has diminished. For this reason, the end-tidal P_{O_2} deviates more widely from the true alveolar value than does the end-tidal P_{CO_2}.

From the above discussion, one can conclude that the requirements for the indirect calculation of the alveolar P_{O_2} by the method of Riley and Cournand (7) can under ideal circumstances be satisfied in normal men. Nevertheless, the method is quite sensitive to fluctuations of the pattern of breathing and the ideal circumstances required are so strict that they may commonly not be achieved (24). Moreover, to apply the method in diseased persons still requires proof that there is no barrier to the diffusion of CO_2 across the alveolar membrane in these subjects. Available data from this laboratory can be interpreted to show that in some pathological conditions diffusely involving the lung the arterial P_{CO_2} actually exceeds that of the alveolar gas.

The Aa Difference in Normal Men at Rest and during Exercise

METHODS

Arterial blood and expired gas samples were obtained at rest and during exercise from 36 normal males who were also extensively studied with regard to other pulmonary functions. Their mean age was 41 years, the extremes being 23 and 60 years.

The subjects were studied at least one hour after their last meal. After the subject rested on a bed for 20 minutes, an indwelling No. 20 needle was placed in a brachial or radial artery. For experiments under resting conditions, another 10 minutes were allowed to elapse before the subject began to breathe through a mouthpiece connected to one-way valves, flushing for 5 minutes the expiratory side of the rubber tubing leading to Douglas bags (previously rinsed with room air). A preliminary expired air collection of two or six minutes' duration was then made. Another bag was so connected that without loss of expired gas a 75 to 120-second collection could be made simultaneously with the slow and even sampling of 15 cc. of arterial blood. The gas was collected beginning at the first inspiration after blood appeared in the syringe and ending with the first inspiration after blood sampling was completed. Respirations were counted during this accurately timed period.

In exercise experiments, a grade and speed (8 to 12 per cent, 3 to 3.5 mph.) on a motor-driven treadmill were chosen such that the subject's O_2 uptake was approximately 75 per cent of the maximum of which he was capable. With the arterial needle in place, the subject walked for 5.5 to 6 minutes, rinsing the Henderson-Haggard trap (20) for the continuous collection of end-tidal gas, and achieving a state of exercise such that nearly constant values for minute ventilation, O_2 uptake, R_E and pulse rate were reached. During the last 60 to 100 seconds of the walk, 15 cc. of arterial blood were withdrawn simultaneously with the collection of expired and end-tidal gas, and respirations were counted during this accurately timed period.

Expired gas was measured and sampled and was analyzed in duplicate in the Haldane apparatus. Checks within 0.04 vol. per cent for O_2 and CO_2 were required. Arterial blood, collected in a syringe whose dead space was obliterated by a heparin-sodium fluoride mixture, was analyzed in duplicate for O_2 and CO_2 content by the method of Van Slyke and Neill (25) within an hour after blood-sampling. The syringe was rotated inside

TABLE III

*Respiratory and arterial blood measurements in 19 subjects at rest**

Case	Age	MV	R_E	O_2v	O_2 Uptake	Art. % sat.	Art. CO_2 content	Art. pH	Art. P_{CO_2}	$\frac{V_D}{V_T}$	Alv. P_{O_2}	Art. P_{O_2}	Aa diff.
		L./min.			*L./min./ m²*		*Vol. %*		*mm. Hg*		*mm. Hg*	*mm. Hg*	*mm. Hg*
76	26	6.01	.75	22.3	.139	97.1	46.3	7.43	39	.22	91	86	5
2	32	8.80	.92	35.2	.152	97.7	45.7	7.47	35	.33	104	96	8
18	60	11.20	.89	38.0	.160	98.5	44.5	7.43	36	.38	101	89	12
79	24	7.00	.77	23.8	.142	96.8	49.9	7.43	40	.23	93	83	10
78	23	7.00	.80	23.6	.146	95.9	49.8	7.45	44	.32	89	85	4
1	31	9.00	.85	30.0	.163	95.6	47.2	7.43	39	.28	97	81	16
82	31	5.58	.85	27.2	.126	97.3	50.2	7.44	37	.26	100	92	8
89	30	9.50	.77	29.3	.152				39	.35	92	81	11
87	35	6.90	.86	25.7	.134	98.6	56.5	7.44	42	.25	95	88	7
15	55	7.10	.75	26.8	.150	96.8	49.2	7.43	40	.34	90	70	20
77	23	7.00	.76	19.3	.168	94.7	49.2	7.43	37	.10	94	91	3
80	28	2.34	.73	20.9	.058		50.3	7.45	32	.00	100	92	8
84	32	5.16	.75	23.8	.121		48.8		42	.31	87	83	4
94	52	9.44	.79	30.5	.149		49.1		41	.37	91	80	11
96	53	4.75	.76	27.6	.086		49.3		42	.38	89	74	15
90	38	6.80	.87	25.1	.132		48.0		39	.20	99	86	13
86	32	9.50	.87	30.0	.145		49.2		33	.19	103	86	17
81	31	6.27	.77	23.8	.142		52.4		41	.28	88	88	0
88	35	7.18	.90	27.6	.146				39	.28	99	86	13
Mean		7.19	.811	26.87	.137	96.90	49.15	7.44	38.8	.266	94.8	85.1	9.7
S.D.		2.06	.061	4.65	.0268	1.24	2.68		3.16	.097	5.35	6.25	5.27

* In the first seven subjects all analytical criteria (see Discussion) were satisfied. The mean Aa difference in these subjects was 9.0 mm. Hg with a standard deviation of 3.61 mm. Hg.

a refrigerator in the interval between sampling and analysis. Oxygen capacity was determined by the method of Sendroy (26) with slight modifications (1). The pH of arterial blood plasma was determined by the method of Hastings and Sendroy (27). Arterial O_2 and CO_2 tensions were determined in duplicate within nine minutes after blood sampling by the method of Riley, Proemmel, and Franke (28) in 31 analyses and by a modification of this method elsewhere described (1) in 22 analyses. Checks within 6 mm. Hg were required.

Minute ventilation (MV) was expressed as liters of expired gas per minute at 37° C., ambient pressure, and saturated with water vapor at Tissot temperature. Tidal volume (V_T) = MV/respiratory rate. Oxygen uptake was expressed in liters of O_2 (STPD) per minute. The O_2 ventilation equivalent (O_2v) was defined as MV/O_2 uptake. Alveolar P_{O_2} and the physiological dead space (V_D) were calculated by formulas 12 and 13 in the paper by Riley and Cournand (7). In calculating V_D/V_T the apparatus dead space was not subtracted from V_T.

RESULTS

The results of the studies at rest are shown in Table III. The mean of the calculated alveolar O_2 tension was 94.8 mm. Hg or 13.2 per cent of the mean barometric pressure in this laboratory (elevation 1,600 feet). The mean of the arterial P_{O_2} was 85.1 mm. Hg. The alveolar-arterial O_2 tension differences averaged 9.7 mm. Hg, the extremes being 0 and 20 mm. Hg.

The studies performed on normal men during exercise are shown in Table IV. The mean of the calculated alveolar O_2 tension was 102.1 mm. Hg or 14.2 per cent of the mean barometric pressure. The mean of the arterial P_{O_2} was 82.5 mm. Hg giving a mean for the Aa difference of 19.6 mm. Hg with extremes of 11 to 27 mm. Hg.

At rest the variations from subject to subject in minute ventilation and O_2 uptake per square meter of body surface were as anticipated. The variations in the O_2 ventilation equivalent and R_E were outside the limits of analytical error. The variations in alveolar and arterial gas tensions were somewhat greater than should result from analytical error alone (1). In an effort to account for these variations, correlation studies were carried out. Table V shows that at rest, as expected, there was a positive correlation between the minute ventilation and R_E. A more definite positive correlation existed between the resting ventilation equivalent (O_2v) and R_E indicating that even slight overbreathing resulted in an elevation of R_E. There was a definite tendency during rest for over-breath-

TABLE IV

Respiratory and arterial blood measurements in 34 subjects during moderately severe treadmill exercise *

Case	Age	Mph.	MV	R_E	O_2v	O_2 uptake	Art. % sat.	Art. CO_2 content	Art. pH	Art. P_{CO_2}	$\frac{V_D}{V_T}$	Alv. P_{O_2}	Art. P_{O_2}	Aa diff.
		% grade	L./min.			L./min./m^2		Vol. %		mm. Hg		mm. Hg	mm. Hg	mm. Hg
76	26	3.5/12	59.5	1.02	27.7	1.11	99.4	39.7	7.37	35	.08	105	81	24
2	32	3.5/10	61.6	1.07	32.4	1.15	99.1	32.8	7.32	35	.17	109	89	20
18	60	3.5/8	60.2	1.02	35.1	.93	98.4	39.8	7.43	34	.17	108	91	17
79	24	3.5/12	68.2	1.06	27.5	1.20	94.9	35.7	7.35	38	.13	106	94	12
78	23	3.5/12	69.4	1.04	25.9	1.32	95.9	41.3	7.40	39	.10	103	85	18
87	35	3.0/10	35.4	.92	19.6	.90	90.6	53.6	7.39	49	.16	100	80	20
15	55	3.5/8	59.3	.99	30.2	1.10	98.1	40.4	7.43	36	.13	105	85	20
84	32	3.5/10	51.8	.92	24.2	1.19		42.4	7.40	37	.11	103	80	23
83	32	3.5/10	50.4	1.02	29.0	.99	92.8	41.3	7.37	37	.17	105	86	19
3	40	3.5/12	44.3	.97	21.8	1.16	93.9	47.0	7.35	40	.22	99	75	24
4	44	3.5/10	58.2	1.00	28.7	1.14	91.3	42.7	7.35	45	.31	93	74	19
92	44	3.5/8	66.8	.97	28.0	1.11	94.5	40.1	7.36	38	.20	102	81	21
25	45	3.5/8	33.6	.92	24.8	.82	95.8	47.2	7.40	40	.17	98	86	12
6	46	3.5/10	50.4	1.00	25.6	1.09	92.3	40.9	7.33	39	.12	101	86	15
8	49	3.5/12	53.0	.96	24.2	1.18	91.5	43.6	7.41	41	.15	99	75	24
93	50	3.5/12	63.8	.96	31.0	1.14	92.1	38.7	7.38	31	.12	110	85	25
95	53	3.5/10	52.5	.99	30.8	.96	98.2	42.5	7.43	38	.25	103	91	12
14	54	3.5/10	59.6	.95	26.0	1.18	94.6	42.8	7.40	35	.08	104	82	22
16	55	3.5/8	51.6	1.04	33.1	.94	94.9	39.6	7.43	34	.16	109	89	20
17	59	3.5/8	40.1	.87	23.6	.90	95.3	45.1	7.43	39	.21	96	80	16
89	30	3.5/12	65.3	.93	23.5	1.30				35	.03	104	79	25
82	31	3.5/12	61.6	1.22	36.9	1.05	93.6	32.9	7.30	39	.18	108	88	20
1	31	3.5/12		.99	28.4		94.6	39.9	7.43	32	.04	110	84	26
77	23	3.5/12	71.8	1.03	25.6	1.30	97.4	39.7	7.36	40	.11	103	78	25
80	28	3.5/8	35.3	.91	22.6	.81	92.9	48.2	7.45	36	.03	100	80	20
90	38	3.5/10	60.6	.97	26.0	1.14	94.7	40.1	7.39	32	.01	108	83	25
97	59	3.5/8	39.5	.87	25.8	.85	96.4	48.7	7.40	43	.30	91	76	15
9	49	3.5/8	50.0	.97	25.2	1.04	94.5	41.1	7.42	43	.06	96	84	12
10	50	3.5/8	45.6	.92	25.5	1.09	94.6	45.7	7.43	32	.00	106	79	27
5	45	3.5/12	71.6	.92	28.1	1.21	96.1	36.6	7.41	38	.24	100	75	25
85	32	3.5/10	75.6	.93	25.2	1.35	94.6	38.2	7.35	44	.27	95	73	22
94	52	3.5/8	44.9	.88	22.3	.98		47.4		40	.13	98	87	11
96	53	3.5/8	55.0	.92	29.4	.95		43.5		40	.29	99	86	13
86	32	3.5/8	53.2	.87	25.6	.95		47.9		38	.22	95	77	18
Mean	41.5		55.14	.971	27.04	1.077	94.93	42.00	7.388	38.0	.151	102.1	82.5	19.6
S.D.			11.02	.071	3.79	.144	2.33	4.55		3.98	.082	5.07	5.41	4.74

* In the last 11 subjects listed not all analytical criteria were satisfied. The mean Aa difference in these 11 subjects was 19.4 mm. Hg.

TABLE V

The relation of the minute ventilation and the oxygen ventilation equivalent to the respiratory quotient and alveolar and arterial P_{O_2} in 19 subjects at rest and 34 subjects during exercise

	Resting				Exercise			
	N	"r"	S.E.	P	N	"r"	S.E.	P
MV vs. R_E	19	.546	.166	.01	33	.440	.143	.01
MV vs. Alveolar P_{O_2}	19	.276	.056	>.1	33	.353	.155	.05
MV vs. Arterial P_{O_2}	19	−.046	.024	>.1	33	.021	.177	>.1
MV vs. Aa difference	19	.337	.209	>.1	33	.349	.155	.05
O_2v vs. R_E	19	.673	.129	<.001	34	.683	.093	<.001
O_2v vs. Alveolar P_{O_2}	19	.473	.183	.05	34	.548	.122	.001
O_2v vs. Arterial P_{O_2}	19	.003	.236	>.1	34	.546	.122	.001
O_2v vs. Aa difference	19	.479	.182	.05	34	−.035	.174	>.1

TABLE VI

Comparison of mean values obtained at rest (19 cases) and during strenuous exercise (34 cases)

	Rest	Exercise	Difference of means	S.E. of difference of means
Calc. alv. P_{O_2}	94.8	102.1	7.3	1.503
Art. P_{O_2}	85.1	82.5	2.6	1.706
Aa difference	9.7	19.6	9.9	1.456
% O_2 sat.	96.90	94.93	1.97	0.583
CO_2 content	49.15	42.00	7.15	1.024
Art. P_{CO_2}	38.8	38.0	0.8	0.995
O_2v	26.87	27.04	0.17	1.249
V_D/V_T	.266	.151	.115	0.027

ing, as defined by an increased O_2v, to be associated with an increased Aa difference. This increase resulted from an elevated calculated alveolar P_{O_2} in association with over-breathing. During exercise, these relationships were similar except for the fact that the Aa difference bore no relationship to the O_2v.

The mean values obtained at rest are compared with those of the exercise studies in Table VI. The statistically significant increase in the Aa difference was largely the result of the marked rise in alveolar P_{O_2} although a slight but not significant decrease in arterial P_{O_2} also occurred. The decrease in the per cent saturation of the arterial hemoglobin with exercise, though small, was a significant one. The decrease in CO_2 content of 7.15 vol. per cent was highly significant. The mean arterial P_{CO_2} showed an insignificant difference between the resting and exercise values. The mean O_2v was virtually identical at rest and during exercise.

The ratio of physiological dead space to tidal volume was significantly lower during exercise than at rest; under both conditions, this ratio had a wide range of values. Occasionally, both during rest and exercise, the arterial P_{CO_2} was so slightly greater than the expired P_{CO_2} that the calculated physiological dead space was zero.

DISCUSSION

The difference between alveolar and peripheral arterial O_2 tension has been reported (29–31) to lie between 0 and 25 mm. Hg in normal resting subjects. It is generally agreed that the P_{O_2} of blood removed from the peripheral arteries can now be measured directly with an accuracy of ± 2 mm. Hg and that, if determined immediately after obtaining the blood sample, the measurement faithfully represents the P_{O_2} of blood flowing through the peripheral arteries. Unfortunately, in earlier studies, the arterial P_{O_2} was measured by indirect methods in which the error may be considerably greater; hence, the variation of Aa difference reported in the literature may in part be accounted for on the basis of the technique for measuring arterial P_{O_2}. Previous methods for measuring an alveolar P_{O_2} as well as the values obtained have varied considerably. For reasons discussed earlier in this paper, we believe that direct sampling fails from both a spatial and temporal point of view to give a faithful moiety of the gas from or representative of that within the alveoli of the lungs. We prefer the indirect method of measuring an alveolar P_{O_2} even though the method is based upon assumptions that at times are not fulfilled in actual practice. Moreover, we prefer to designate the value as *an* alveolar P_{O_2} rather than *the* alveolar P_{O_2} since the latter at any one moment undoubtedly has various values at different places within the lungs, all of which vary during the course of each respiratory cycle. Furthermore, it must be apparent that the indirectly calculated alveolar P_{O_2} can be considered as *representative* of alveolar gas only in the limited sense that arterial P_{CO_2} actually represents alveolar P_{CO_2}. In essence, the "alveolar P_{CO_2} and P_{O_2}" obtained by indirect methods are an integration of spatially and temporally fluctuating alveolar P_{O_2}'s and P_{CO_2}'s which are so related as to give the actual arterial P_{CO_2} and expired air R.Q. that is obtained by direct measurement. What is actually done is to measure directly the gas tensions of expired air and arterial blood and conclude that in order for the blood leaving the lungs and the R.Q. of expired air to be as actually measured, the integrated alveolar O_2 tension to which the blood was exposed must have been as calculated.

Our data clearly support those who contend that the indirectly calculated alveolar P_{O_2} is normally higher than the arterial P_{O_2}. As will be discussed later, the random character of the variation in the calculated alveolar P_{O_2} is evidence that the higher alveolar P_{O_2} is not purely a technical error.

The variation in the Aa difference among normal recumbent individuals (Table III) is somewhat greater than that reported by Lilienthal,

TABLE VII

The results of all arterial blood studies that have been performed on Subject No. 84 *

Condition	Date	MV	V_T	R_E	O_2V	O_2 uptake	Art. P_{CO_2}	$\frac{V_D}{V_T}$	Alv. P_{O_2}	Art. P_{O_2}	Aa diff.
		L./min.	*cc.*			*L./min./m²*	*mm. Hg*		*mm. Hg*	*mm. Hg*	*mm. Hg*
Resting	9/ 8/47	4.81	610	.71	23.8	.112	37	.22	94	83	11
Resting	11/12/47	5.17	638	.75	23.8	.113	42	.31	87	83	4
Resting	11/13/47	7.78	670	.77	28.4	.152	45	.42	85	78	7
Resting	11/13/47	6.70	770	.71	25.5	.146	47	.45	79	79	0
Resting	11/28/47	5.75	570	.64	24.4	.131	40	.37	82	74	8
Resting	9/14/47	5.71	794	.73	24.3	.131	39	.33	91	83	8
Resting	9/14/47	5.98	786	.73	23.1	.144	44	.34	85	83	2
Resting	9/14/47	6.36	795	.78	25.4	.139	40	.30	93	88	5
Resting	9/14/47	6.02	782	.75	24.1	.139	40	.29	91	85	6
Resting	9/14/47	5.73	726	.73	24.1	.132	42	.32	87	87	0
Resting	12/ 8/49	6.73	750	.77	24.7	.151	41	.31	90	81	9
Mean		6.07	716	.734	24.69	.136	41.5	.337	87.6	82.2	5.5
2% Grade	10/16/50	29.4	1960	.94	23.6	.677	43	.20	99	90	9
2% Grade	10/18/50	30.1	2110	.90	24.0	.682	41	.21	98	85	13
2% Grade	3/12/51	31.3	2060	.88	23.0	.740	41	.18	97	83	14
2% Grade	3/27/51	38.0	1960	.93	26.6	.775	39	.21	101	91	10
6% Grade	10/16/50	47.1	1860	1.01	28.0	.934	39	.18	105	88	17
6% Grade	10/18/50	40.1	1950	.98	26.7	.836	38	.14	104	88	16
10% Grade	8/10/48	51.8	2630	.92	24.2	1.160	37	.11	102	80	22
10% Grade	10/16/50	62.5	2320	1.05	29.1	1.190	39	.19	106	92	14
10% Grade	10/18/50	62.0	2660	1.03	29.7	1.160	33	.09	110	86	24
16% Grade	12/ 9/52	116.0	2970	1.13	42.8	1.480	30	.23	115	89	26

* The speed of treadmill walking was 3.5 mph.

Riley, Proemmel, and Franke (30) in six men under similar experimental conditions. To what extent are our results influenced by (a) analytical errors, (b) failure to fulfill the experimental conditions required for the valid calculation of alveolar P_{O_2}, (c) physiologic differences among normal men caused by psychological stimuli associated with taking of biological samples, and (d) actual physiologic differences between normal persons?

In order to explore the influence of analytical errors, it is necessary to eliminate so far as possible the influence of factors (b), (c), and (d). With this in mind, 12 separate determinations of the alveolar-arterial O_2 tension difference were made in the same trained normal subject (Case 84) at rest. The subject was thoroughly accustomed to breathing through a mouthpiece and showed somewhat smaller minute to minute variations in his R_E than most trained subjects. The results of these experiments (Table VII) show that even when factors (b), (c), and (d) are held as constant as possible the variation of the alveolar-arterial O_2 tension difference was of the same order as in the entire group of persons studied as shown in Table III. The analytical error of our blood gas tension determinations averages about ± 2 mm. Hg both for O_2 and CO_2 (1). Errors of this magnitude can result in an error of approximately ± 4 mm. Hg in the difference between calculated alveolar and determined arterial O_2 tension. Since the mean of this difference, repeatedly determined in the same subject, was 5.5 mm. Hg with a standard deviation of 3.77 mm. Hg, it would appear that analytical errors account in part, but not entirely, for the variations observed.

It has been suggested (7) that technical errors can be minimized by consideration of other data related to blood gas tension determinations. The following criteria define an analytically satisfactory experiment in our laboratory:

(i) The directly determined P_{CO_2} must be within 4 mm. Hg of that calculated (32) from CO_2 content, O_2 capacity and pH of arterial blood.

(ii) The physiological dead space must be greater than 50 cc. at rest and 100 cc. during exercise.

(iii) The pH calculated (32) from the directly determined P_{CO_2}, CO_2 content and O_2 capacity of arterial blood must agree within 0.03 pH units with the directly determined pH.

(iv) The directly determined P_{O_2} must lie within 15 per cent of that calculated from the standard dissociation curve (8), the O_2 content and capacity and the pH of arterial blood.

Although these criteria are helpful in discovering gross errors, the alveolar-arterial O_2 tension differences obtained in the experiments in which all of these criteria were satisfied were not significantly different from the figures for the subjects as a group as shown in Tables III and IV.

There is little doubt that the alveolar and arterial CO_2 tensions are virtually equal in normal resting men. Whether or not it can be assumed that R_E exactly equalled the CO_2–O_2 exchange ratio at the "alveolar membrane" during the blood sampling period in our resting subjects is open to question, even though a period of rest long enough to obtain stabilization of the minute ventilation (33) was allowed to elapse before blood sampling began. For purposes of obtaining information for such short periods of sampling, we have routinely determined the expired R_E both before and during the blood sampling period. The mean difference between the first and second R_E of 167 clinical subjects was 0.0393, a difference more than twice that to be expected from errors of Haldane analysis; the standard deviation of this difference was 0.0375. These data plus the minute-to-minute variations of R_E shown for the trained subjects in Table I are clear evidence that a steady state is not commonly obtained under experimetal conditions. If, in addition to the effect of analytical errors, the calculated alveolar P_{O_2} is also in error because of transient discrepancies between the R_E of expired gas and that of pulmonary blood, the observed range of variation of the alveolar-arterial O_2 tension difference in normal men at rest is readily explainable. However, this in no way invalidates the fact that an Aa difference normally exists at rest since both the analytical errors and the expired R_E variations are of a random character.

The fact that R_E varies from minute to minute both in patients and in normal subjects has an obvious bearing on the technique for collecting expired gas and arterial blood. When, for example, expired gas is collected for a longer period of time than arterial blood is sampled, the calculated alveolar P_{O_2} will be in error to the extent that R_E for the whole period of gas collection differs from the R_E of the period of arterial blood sampling.

In attempting to find relationships between the blood gas data and the other measurements made simultaneously, we have observed that when overbreathing at rest occurs, as indicated by an elevated O_2v, the alveolar-arterial O_2 tension difference tends to be elevated both in health and disease. It is known that voluntary hyperventilation at sea level can raise the alveolar O_2 tension without producing a proportionate rise in the arterial P_{O_2} (34) or arterial O_2 saturation (35). Dill and Penrod have reported a similar relationship occurring in subjects at simulated altitudes (36) and pointed out that the explanation for this phenomenon is not clear. Since the resting minute ventilation of normal men breathing through a mouthpiece is often out of proportion to the metabolic demands of the body, probably because of psychological stimuli, it is reasonable to attribute some of the variations in the alveolar-arterial O_2 tension difference seen in Table III to the variable respiratory response of each individual to the experimental procedure.

In view of factors (a), (b), and (c) it is questionable whether under resting conditions a single determination of the alveolar-arterial O_2 tension difference can be considered characteristic for a given normal individual. We believe it will be necessary to make multiple determinations of the Aa difference in each of several individuals in order to disclose the extent to which persons truly differ from one another in this respect. Such data are not available.

The variation in the Aa difference in normal exercising men as expressed by the standard deviation of 4.74 is slightly less than the variation in this measurement at rest despite the fact that the exercise studies were carried out at various grades and speeds of treadmill walking. To investigate the effect of the severity of exercise on the Aa difference and other measurements, the exercise studies of Table VII were performed. The Aa difference rose progressively in this subject with increasing exercise primarily as a result of the increasing calculated alveolar P_{O_2}. This rising alveolar P_{O_2} in turn resulted from a decrease in the ratio V_D/V_T. Since the analytical methods were the same in resting as in exercise studies, and since some variation among normal subjects would be expected to

TABLE VIII

Mean values in normal subjects at rest and during varying amounts of exercise

Subjects	No. of determinations	Condition	O_2 uptake	Mixed venous % sat.	Aa diff.	% Venous admixture*
			L./min./m²		*mm. Hg*	
Of Table III	19	Rest	.137	78	9.7	6.4
Of Table IV	34	Moderate exercise	1.077	47	19.6	5.5
Subject No. 84	11	Rest	.136	79	5.5	4.7
	4	Light exercise	.719	49	11.5	3.5
	2	Moderate exercise	.880	47.5	16.5	4.0
	3	Heavy exercise	1.170	45	20.0	5.0
	1	Exhausting exercise	1.480	30	26	4.5

* The % venous admixture was calculated as follows:

$$\% \text{ Venous admixture} = \frac{\text{Alveolar capillary \% sat.} - \text{Arterial \% sat.}}{\text{Alveolar capillary \% sat.} - \text{Mixed venous \% sat.}} \times 100.$$

The alveolar capillary % saturation was calculated from the alveolar P_{O_2} and the standard dissociation curve (8). See Text.

result from their exercising at different speeds and grades, some explanation is required for the relatively low standard deviation of the exercise Aa difference.

In the first place, as seen in Table I, there is less minute-to-minute change in minute ventilation and R_E during exercise than at rest. For this reason it is likely that during exercise the conditions for the valid calculation of alveolar P_{O_2} are more easily fulfilled than in the resting state. Secondly, there is less variation among normal individuals in the O_2 ventilation equivalent during exercise than at rest. It seems reasonable to conclude, therefore, that during exercise the alveolar P_{O_2} is less subject than at rest to errors caused by failure to maintain a steady state. The respiratory drive during exercise appears to be less affected by psychic stimuli than at rest; hence the value for the Aa difference is more likely to be characteristic for a given individual when he is exercising than when he is at rest. This conclusion is borne out by the results of the exercise studies on a single subject as seen in Table VI where, except in one instance, repeated determinations of the Aa difference under the same exercise conditions agreed more closely than they did at rest.

An Interpretation of the Normal Aa Difference

The experimental finding that alveolar O_2 tension exceeds that in the arterial blood of normal men has been attributed to:

1) Experimental errors involved in sampling alveolar gas and analyzing arterial blood.
2) A change in the physico-chemical state of the blood in transit from lung to artery.
3) Failure of pulmonary capillary blood to reach alveolar O_2 tension ("membrane factor").
4) The admixture of venous blood (*via* shunts) or partially oxygenated blood (*via* poorly ventilated alveoli) with pulmonary capillary blood ("venous admixture").

For reasons discussed earlier, the first explanation appears to be inadequate to explain the Aa difference observed in the present study. Considerable evidence against the validity of the second explanation has been marshalled by Roughton (22).

It appears likely (37) that equilibrium with respect to O_2 is normally attained between alveolar capillary blood and alveolar gas in resting sub-

jects (38). Whether or not this is true during heavy exercise is open to question since the time spent by pulmonary blood in the alveolar capillaries might be insufficient for complete equilibrium to be reached.

In the formulation by Riley and Cournand (7), both the "membrane factor" and the influence of venous admixture are dealt with in detail as explanations for an Aa difference determined under various conditions in normal persons. Riley (39) considers that, in young normal resting subjects breathing air at sea level, virtually all of the Aa difference is to be accounted for by venous admixture, and that this is the case during exercise not involving an O_2 uptake of greater than 2,000 cc. per min. In Table VIII the percentages of venous admixture have been calculated from the Aa differences obtained in 36 normal subjects at rest and during exercise, one of whom was studied repeatedly at several different stints of work. The hemoglobin saturation of mixed venous blood was estimated by assuming that values for arterial-venous O_2 difference were related to the O_2 uptake in the same way as was reported by other investigators (40) for conditions at rest and during moderate exercise. For heavy exercise, the data of Asmussen and Nielsen (41) were used. It can be seen that in the group of 36 subjects the calculated per cent venous admixture declined slightly during exercise while in Subject No. 84 it remained approximately constant at five different levels of metabolic activity. The calculations suggest that it is not necessary to postulate a "membrane factor" to explain the increased Aa difference observed in normal subjects during exercise. Indeed, if one wishes to postulate a "membrane factor" during exercise, the per cent venous admixture must be assumed to be reduced below the figure obtained at rest. There is no evidence for or against the assumption that venous admixture diminishes during exercise.

It is of interest that the observed tendency of the Aa difference to increase with slight hyperventilation at rest (Table V) is readily explained on the venous admixture hypothesis by a consideration of the shape of the oxyhemoglobin dissociation curve. If the per cent venous admixture and the arterio-venous oxygen difference are not greatly changed by hyperventilation, the fact that the alveolar capillary and arterial points have moved to a flatter portion of the dissociation curve necessitates an increase in the Aa difference.

It remains to consider whether or not alveolar and arterial O_2 tensions can be used as sensitive criteria for the normality of pulmonary O_2 transport. As seen in Table III and IV, the variability of these measurements among normal persons is greater than that of the per cent arterial hemoglobin saturation. On this basis, it would appear that arterial P_{O_2} cannot be used to narrow the limits of normality of arterial blood oxygenation. Furthermore, the variability of the Aa difference among normal persons is of the same order as the variability of either alveolar or arterial P_{O_2}. It remains to be demonstrated that comparisons between these measurements in normal subjects and those obtained in diseased persons will prove to be of greater value as criteria for the normality of O_2 transfer than the more usual determinations of arterial per cent hemoglobin saturation.

SUMMARY

1. The calculation of alveolar O_2 tension from expired gas and arterial blood tension determinations provides a representative value for the P_{O_2} to which pulmonary capillary blood is exposed in normal men breathing air at rest and during exercise if certain experimental conditions are met.

2. These conditions have been examined.

3. The mean alveolar-arterial O_2 tension difference is 9.7 mm. Hg (S.D. $\pm$ 5.3 mm. Hg) at rest and 19.6 mm. Hg (S.D. $\pm$ 4.7 mm. Hg) during moderately strenuous exercise in normal men breathing air at 1600 feet above sea level.

4. The variability of the Aa difference in normal men at rest is not necessarily dependent on factors characteristic for each individual. This difference is significantly affected by variations in the calculated alveolar P_{O_2}, which in turn is influenced by the ratio of the minute ventilation to the O_2 uptake.

5. The conditions required for calculating an alveolar P_{O_2} are more closely approached and the O_2 ventilation equivalent varies less among normal persons during exercise than at rest. For these reasons, an Aa difference measured during exercise is likely to be more characteristic for a given individual than when measured during rest.

6. The normal Aa difference during both rest and exercise can be accounted for on the hypothe-

sis that peripheral arterial blood is normally composed of a mixture of completely oxygenated blood and of incompletely oxygenated blood which has either by-passed alveolar structures or perfused poorly ventilated alveoli.

7. The variability of the alveolar and arterial O_2 tensions and of the difference between them at rest and during exercise is greater in normal subjects than is the variability of the arterial per cent hemoglobin saturation.

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