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Alterations in Ventilation-Perfusion Relationships in the Lung after Breathing Inert Dust or Bronchoconstrictor Aero- sols and after Short Periods of Voluntary Hyperventilation

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The increase in airway resistance that follows the breathing of fine inert dust was first demonstrated by DuBois and Dautrebande (1), who also showed that an aerosol of carbachol had the same effect. The compliance of the lungs was reduced, which led these authors to conclude that the increased airway resistance was unevenly distributed. Constantine and associates (2) confirmed the increased airway resistance in similar experiments and also noted an increase in intrathoracic gas volume, which they attributed to trapping of gas. McDermott (3) found a significant increase in airway resistance after breathing similar dusts at concentrations almost certainly less than those used by the previous workers and more comparable to the concentrations encountered under certain industrial conditions. She also commented on the considerable individual variation in response.

The first part of the present study had two main objectives, the first of which was to determine the extent to which these inhaled materials altered the distribution of alveolar ventilation and to observe the effects this had upon respiratory gas exchange in the lungs. Of at least equal importance was the possibility that the experiments might reveal something of how the distribution of alveolar perfusion responds to an acute alteration in the distribution of alveolar ventilation, and this has influenced the design of the experiments.

During these experiments the possibility arose that the observed effects might result from the associated moderate hyperventilation. A preliminary observation lent support to the idea that hyperventilation was followed by an increase in

physiological dead space, and this led to the second series of experiments. The results, which have already been reported briefly (4), showed a prolonged increase in physiological dead space after hyperventilation in the sitting position. This was prevented by substituting a mixture containing carbon dioxide for air during the period of hyperventilation and was much less evident when the subjects were supine.

Methods

Respiratory gas exchange was investigated by the measurement of the alveolar-arterial difference in oxygen tension (A-aD) and physiological dead space. Expired gas was collected in a Tissot spirometer for 2 minutes and was analyzed by the Scholander method. During this time three samples of blood for estimation of P_{O_2} and two samples for P_{CO_2} were obtained from a needle in the brachial artery, sampling extending over the whole of the 2-minute period. The P_{O_2} of arterial blood was measured within 10 minutes of sampling by a polythene-covered combined electrode system (5), the standard deviation of an estimate of oxygen tension in the region of 100 mm Hg being 0.7 mm Hg. Arterial P_{CO_2} was measured by a modification of the interpolation method of Åstrup (6). The blood was centrifuged anaerobically at 38° C, and after the initial pH reading, the plasma was equilibrated at three known carbon dioxide tensions.

The alveolar oxygen tension was calculated from the alveolar gas equation, assuming arterial carbon dioxide tension to equal alveolar carbon dioxide tension. Physiological dead space was calculated from the Bohr equation, with the same assumption concerning P_{aCO_2} . The apparatus dead space was subtracted, and the result has also been expressed as a percentage of the tidal volume (V_D/V_T).

The distribution of alveolar ventilation was studied by the single breath oxygen test (7), the test conditions being standardized as suggested by Kjellmer, Sandqvist, and Berglund (8). The volume of oxygen inspired was 1 L, no inspiratory pause was allowed, and the subject

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expired at a rate between 30 and 60 L per minute. Oxygen was inspired from one spirometer and the subsequent expirate passed to another spirometer, the pulley wheel of which activated two electrical contacts. This caused a break in the recording of nitrogen concentration at 750 and 1,250 ml of expired volume, and results are given as the difference in concentration at these points.

In some subjects anatomical dead space was also measured by the record of nitrogen concentration together with a simultaneous record of expired volume as described by Fowler (9). In these experiments the inspired volume of oxygen was 500 ml. The response time of the nitrogen meter was measured for each series of observations, and the appropriate allowance was also made for the dead space between the lips and the point of gas sampling.

Aerosols of a 2% solution of carbachol (British Pharmacopoeia) in normal saline were produced with a nebulizer (10) driven from a cylinder of compressed air. It was found that 77% of the droplets produced were in the size range 1.0 to 1.5 μ , and 99% were smaller than 2.4 μ . The aerosol was directed towards the mouth, and the subject took from 20 to 30 inspirations in 3 to 5 minutes, care being taken not to swallow any of the solution which might collect in the mouth.

Calcium carbonate dust was dispersed in the early experiments by directing a jet of air onto the loosely packed powder in a jar. Later a more satisfactory cloud was produced with the Wright dust-feed mechanism (11) using an air flow rate of 8 L per minute. In each case the cloud passed into a large bottle to allow settling of the larger particles and was then delivered to the subject by a flexible tube of approximately 1.5-cm bore. The subject directed the stream into his mouth and breathed deeply, taking 20 to 30 breaths in about 3 minutes. A study of the particle size of the dust cloud revealed that it was highly aggregated and contained about 120,000 particles per ml in the range 0.5 to 5.0 μ and about 40,000 per ml in the range 0.2 to 0.5 μ .

Subjects studied. The subjects were 43 healthy men and women, without any history of respiratory or other significant disease, free from cough sputum, or other

respiratory symptoms, and ranging in age from 21 to 60 years. They walked to the laboratory and rested for at least 30 minutes before the study commenced. Smoking was not allowed during the hour before the start of the study.

Procedure in bronchoconstrictor and dust studies. All of the measurements were made in the sitting position and when breathing air. Two mouthpieces were suspended close to the subject's mouth so that he could readily change from the circuit used for the single-breath test to that used for the collection of expired gas. After an arterial needle had been inserted in the left brachial artery, the subject performed a few single-breath maneuvers to become familiar with the procedure.

The experimental period started with two control measurements of A-aD and physiological dead space, together with three single-breath tests, extending over 15 minutes. The two types of procedure alternated, and at least 3 minutes elapsed between a single-breath test and the next collection of expired gas. The subject then breathed either carbachol aerosol or calcium carbonate dust. Further 5 to 6 measurements of A-aD and physiological dead space were made during the next hour, the timing of these varying a little from subject to subject. Single-breath tests were interpolated as in the control period. A further group of subjects acted as controls and underwent the same procedure with the exception that they did not breathe either carbachol aerosol or a dust cloud.

Procedure in hyperventilation studies. The subjects were divided into four groups as follows: *Group 1* comprised nine subjects studied before and after hyperventilation, breathing air, in the sitting position. *Group 2* comprised four subjects studied before and after hyperventilation, breathing 3 to 5% carbon dioxide in air, in the sitting position. *Group 3* comprised four subjects studied before and after hyperventilation, breathing air, in the supine position. *Group 4* comprised nine subjects studied before and after hyperventilation, breathing air, in the sitting position, and who were also given an intravenous infusion of angiotensin 30 to 40 minutes later.

Two control measurements were made before hyper-

TABLE I
Respiratory gas exchange under resting conditions over a period of 1 hour*

Time	P _A O ₂	P _a O ₂	A-aD	P _a CO ₂	V _D physiol. BTPS	V _T BTPS	V _D /V _T	\dot{V}_A BTPS	R _E
min	mm Hg	mm Hg	mm Hg	mm Hg	ml	ml	%	L/min	
0-2	106	94.9	11.1	37.1	174	646	26.9	6.8	0.890
9-11	108	95.6	12.4	36.7	186	689	27.0	7.0	0.895
19-21	109	98.1	10.9	35.8	177	643	27.5	7.2	0.942
29-31	109	98.5	10.5	36.1	157	588	26.7	6.9	0.904
39-41	107	93.1	13.9	36.9	181	585	30.9	6.4	0.895
49-51	104	93.2	10.8	38.4	172	560	30.7	6.3	0.866
59-61	103	91.1	11.9	39.0	185	545	34.0	6.1	0.854

* Mean values in five subjects. P_AO₂, alveolar oxygen tension; P_aO₂, arterial oxygen tension. A-aD, alveolar-arterial difference in oxygen tension; P_aCO₂, arterial carbon dioxide tension; V_D physiol., physiological dead space; V_T, tidal volume; \dot{V}_A , alveolar ventilation; R_E, respiratory gas exchange ratio; BTPS, body temperature, pressure, saturated with water.

TABLE II
Individual values for V_D/V_T and A-aD in five subjects sitting at rest during a period of 1 hour*

Subject	V_D/V_T Time (min)						A-aD Time (min)							
	0	10	20	30	40	50	60	0	10	20	30	40	50	60
	%						mm Hg							
1	19.8	18.9	19.2	18.7	17.5	25.3	37.9	1.0	3.0	6.0	4.0	9.0	4.0	9.1
2	31.3	29.8	26.2	25.4	28.7	30.5	33.2	16.1	14.5	19.8	17.3	17.5	16.9	15.0
3	19.9	30.6	30.0	32.0	33.9	34.5	34.9	15.1	15.3	10.5	11.4	13.2	10.0	11.2
4	30.3	29.6	28.9	32.1	31.3	29.8	35.6	4.2	4.0	4.8	4.5	5.6	4.3	4.1
5	33.3	28.5	33.4	30.4	31.9	33.4	28.5	21.4	15.8	14.3	17.3	23.2	19.3	18.3

* Abbreviations as in Table I.

ventilation, and five or more collections were made at intervals from 10 to 70 minutes after hyperventilation. Subjects were encouraged to hyperventilate for 3 minutes by taking deep breaths but without attempting to increase the rate of breathing. In 19 of the 26 subjects the expired gas was collected during hyperventilation in a Douglas bag, and its volume measured; a sample of arterial blood was also taken during the third minute for measurement of P_{aCO_2} . The subjects of group 2 breathed, during hyperventilation, a mixture containing 3 to 5% CO_2 in air, which was delivered from a cylinder through an anesthesia bag acting as a reservoir.

In the subjects of group 4, a slow intravenous infusion of normal saline was set up before measurements started. At a time ranging from 33 to 42 minutes after hyperventilation, a solution of synthetic angiotensin was substituted for the normal saline and was delivered by a constant infusion pump at the rate of 2 μg per minute for 5 to 12 minutes. Further measurements were made during and after infusion.

Results

These are given in the Tables and Figures and are described under several headings below. The mean values for the more important measurements are given for each series of experiments, and, where appropriate, individual values for A-aD and V_D/V_T are also presented.

I. Control observations without inhalation or hyperventilation

The mean results obtained in five subjects in whom measurements were made at rest over a period of an hour without inhalation or hyperventilation are presented in Table I. Individual values for V_D/V_T and A-aD are given in Table II.

TABLE III
Respiratory gas exchange before and after inhalation of carbachol aerosol*

Time†	P_{AO_2}	P_{AO_2}	A-aD	P_{aCO_2}	V_D physiol. BTSP	V_T BTSP	V_D/V_T	\dot{V}_A BTSP	R_E	N_2 difference
min	mm Hg	mm Hg	mm Hg	mm Hg	ml	ml	%	L/min		%
Control	108	106	2.0	36.5	128	592	21.6	6.7	0.958	1.1‡
Control	104	102	3.0	38.6	145	575	25.2	5.6	0.914	
1										1.7
4-6	95.0	74.3	20.7	36.9	126	500	25.2	4.4	0.705	1.9
7										
10-12	96.3	78.2	18.1	39.4	117	492	23.8	4.4	0.724	2.5
12-15										
17-19	102	82.3	19.7	39.1	144	550	26.2	5.1	0.851	2.1
20-29										
36-38	102	92.1	9.9	40.8	136	541	25.1	4.6	0.851	2.1
30-39										1.8
40-49										1.8
50-59										1.8
60-62	101	97.6	3.4	40.5	148	592	25.0	4.9	0.848	1.7
65										

* Mean values in four subjects. Abbreviations as in Table I.

† Time in minutes from end of period of carbachol inhalation.

‡ Mean of 3 measurements in each subject.

TABLE IV
*Individual values for V_D/V_T and A-aD before and after breathing carbachol aerosol and calcium carbonate dust**

Subject	V_D/V_T Time after bronchoconstrictor (min)							A-aD Time after bronchoconstrictor (min)							
	C ₁ †	C ₂	4-6	10-12	17-19	36-38	60-62	C ₁	C ₂	4-6	10-12	17-19	36-38	60-62	
				%							mm Hg				
Calcium carbonate dust	1	14.0	19.8	22.4	29.0	24.0	27.6	26.2	-3.0	-2.8	5.2	-1.5	1.3	-3.1	-8.8
	2	20.5	21.4	22.2	17.1	19.1	18.5	17.4	2.0	7.0	16.8	8.7	10.6	5.0	4.0
	3	36.9	32.6	37.9	40.9	34.1	36.3	39.5	-3.8	0.8	13.8	15.0	9.7	-2.5	-7.9
	4	27.5	25.5	31.8	33.1	34.5	31.4	33.3	-0.3	4.5	15.7	1.8	-1.3	-1.0	-1.4
	5	17.6	18.1	27.1	20.2	27.9	26.6	25.7	7.3	7.5	34.0	35.5	24.1	13.1	11.9
	6	20.5	20.6	25.5	25.5	24.6	16.8	18.9	18.0	18.4	30.9	29.9	18.0	17.0	16.7
	7	28.5	23.9	27.9	24.6	27.6	24.3	24.1	-0.5	3.4	15.9	11.9	5.2	5.5	8.3
	8	19.9	20.9	32.9	30.4	38.1	39.7	30.3	18.0	15.0	23.7	24.0	22.0	12.1	14.9
Carbachol aerosol	1	21.0	23.8	26.9	22.9	30.9		25.0	4.7	6.1	24.5	24.8	22.8		0.9
	2	27.4	28.4	27.0	29.3	33.1	25.1	26.0	1.0	1.0	8.9	9.5	7.7	6.4	1.0
	3	16.6	25.6	24.9	20.4	22.3	26.3	28.9	-0.7	2.6	22.4	17.9	17.0	4.1	2.8
	4	21.2	22.8	21.9	22.7	18.6	23.8	21.1	4.0	1.0	27.3	20.9	29.5	18.5	7.0

* Abbreviations as in Table I.

† C₁ and C₂, first and second control observations.

In describing the results, in the following sections, it has been found helpful to consider the changes at each time interval from the mean of the control observations made before the inhalation of the bronchoconstrictor or before hyperventilation.

The results from Table I have therefore been treated in the same way, the changes at each time interval from the mean of the first and second measurements being calculated. The mean changes in A-aD and V_D/V_T are presented in Figures 2

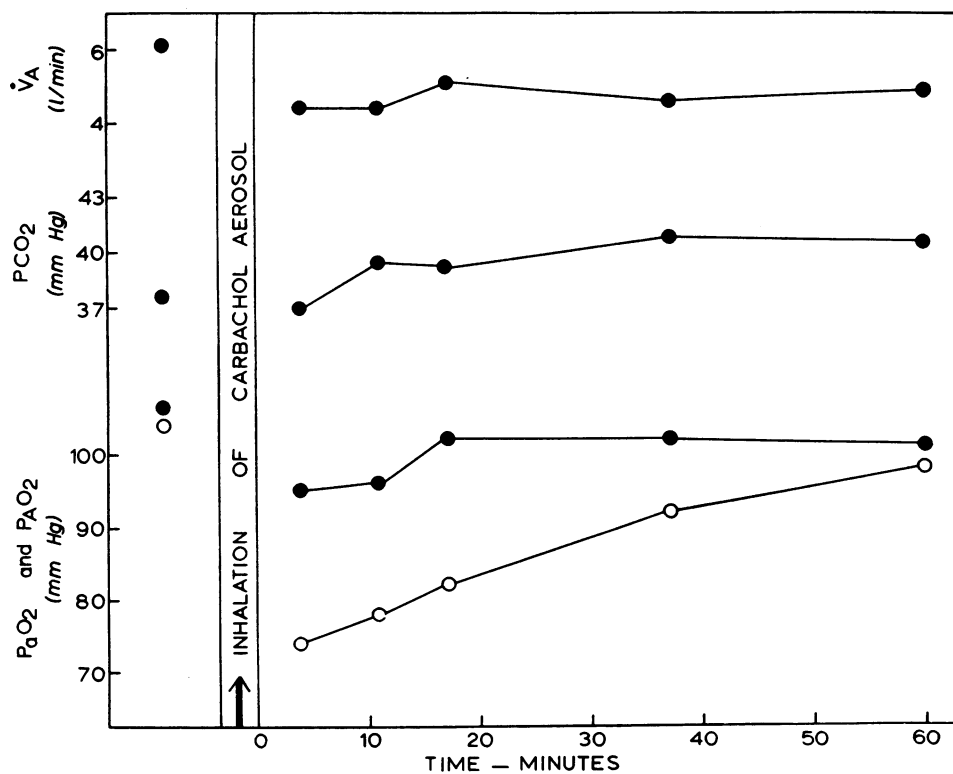


FIG. 1. ALVEOLAR VENTILATION (\dot{V}_A), ARTERIAL CARBON DIOXIDE TENSION (P_{CO_2}), AND ALVEOLAR AND ARTERIAL OXYGEN TENSION ($P_{A_{O_2}}$ AND $P_{a_{O_2}}$) BEFORE AND AFTER INHALATION OF CARBACHOL AEROSOL. Mean values from four subjects.

TABLE V
Values for anatomical dead space before and after breathing dust or carbachol aerosol or voluntary hyperventilation

	Subject	Control	After test procedure
		ml	ml
Calcium carbonate	11	142 [2]*	144 [5]
	12	190 [2]	185 [7]
	13	184 [2]	185 [3]
Carbachol	14	202 [2]	148 [3]
Hyperventilation, breathing air, sitting	15	143 [2]	155 [3]
	16	220 [2]	255 [6]
	17	100 [3]	100 [8]
	18	73 [3]	61 [9]

* Values in brackets indicate number of measurements in each subject.

and 4, together with similar data for nitrogen concentration difference, not given in the Tables. The variations in the A-aD, V_D/V_T , and the nitrogen concentration difference during this time were small; only in the case of V_D/V_T was there even a suggestion of a trend towards the end of the period of observation, and this was not significant.

II. Effects of carbachol aerosol

The mean results in four subjects who breathed carbachol aerosol are given in Table III. Indi-

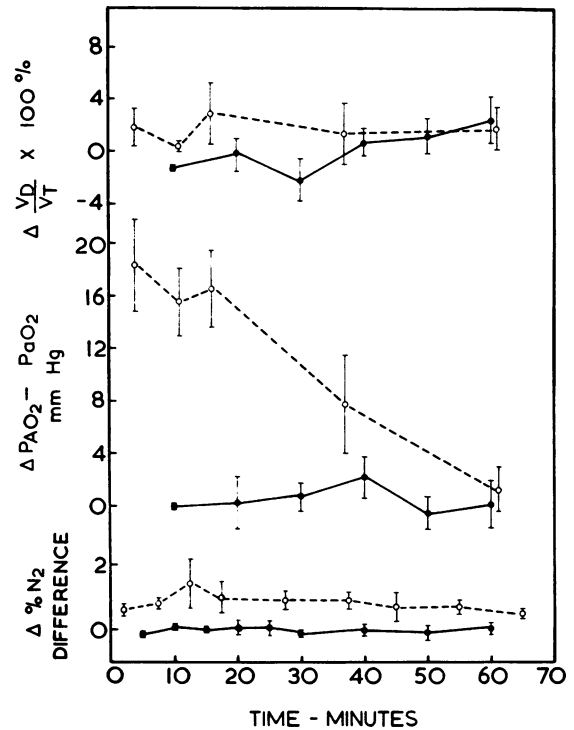


FIG. 2. CHANGES IN PHYSIOLOGICAL DEAD SPACE (V_D/V_T), ALVEOLAR-ARTERIAL DIFFERENCE IN OXYGEN TENSION (A-aD), AND NITROGEN CONCENTRATION DIFFERENCE AFTER INHALATION OF CARBACHOL AEROSOL (BROKEN LINES) AND IN CONTROL SUBJECTS (CONTINUOUS LINES). THE INHALATION WAS COMPLETED AT ZERO TIME. MEAN VALUES FROM FOUR SUBJECTS, \pm SE.

TABLE VI
Respiratory gas exchange before and after inhalation of calcium carbonate dust*

Time†	P_{AO_2}	P_{aO_2}	A-aD	P_{aCO_2}	V_D physiol. BTPS	V_T BTPS	V_D/V_T	\dot{V}_A BTPS	R_E	N_2 difference
	mm Hg	mm Hg	mm Hg	mm Hg	ml	ml	%	L/min		%
Control	101	96.2	4.8	39.3	173	745	23.2	7.0	0.944	1.9‡
Control	98.1	91.3	6.8	39.3	138	603	22.9	5.7	0.815	
2-5	90.2	70.7	19.5	37.3	148	520	28.5	4.4	0.660	3.2
3										
8-11	94.3	78.7	15.6	39.1	161	581	27.7	5.6	0.767	2.1
9										2.6
14										
16-18	96.5	85.3	11.2	40.6	173	604	28.7	5.4	0.820	2.0
15-19										2.4
20-29										
34-36	96.7	90.9	5.8	42.1	173	625	27.7	5.6	0.876	2.4
30-39										2.4
40-49										2.4
50-59										1.6
60-62	97.8	93.1	4.7	40.6	166	617	26.9	5.6	0.867	1.8
70										
80-82	99.0	93.6	5.4	39.9	151	619	24.4	6.1	0.869	1.7
85										

* Mean values in eight subjects. Abbreviations as in Table I.
 † Time in minutes from end of period of inhalation of calcium carbonate.
 ‡ Mean of 3 measurements in each subject.

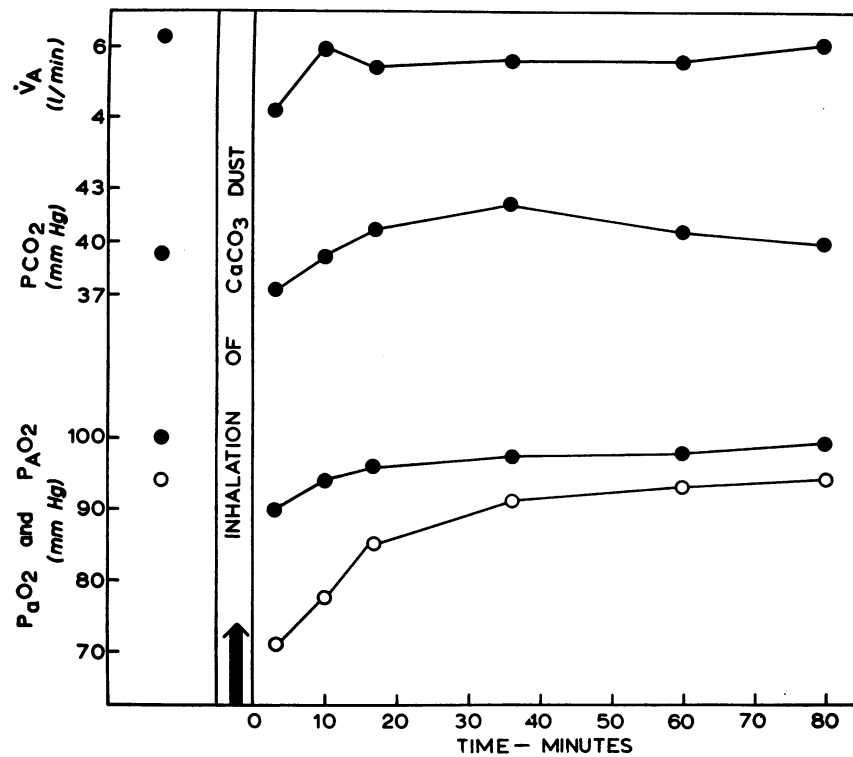


FIG. 3. ALVEOLAR VENTILATION, ARTERIAL CARBON DIOXIDE TENSION, AND ALVEOLAR AND ARTERIAL OXYGEN TENSION BEFORE AND AFTER BREATHING CALCIUM CARBONATE DUST CLOUDS. Mean values from eight subjects.

vidual values for V_D/V_T and A-aD are shown in Table IV. After breathing the bronchoconstrictor, the expired volume fell as also did the alveolar ventilation. Tidal volume decreased at first and then returned towards the control value. The respiratory exchange ratio decreased, but there was no significant change in P_{aCO_2} . These features are illustrated in Figure 1, which also shows the fall in alveolar oxygen tension associated with the decreased alveolar ventilation. Arterial oxygen tension, however, fell much more than the alveolar tension with a resultant increase in A-aD which had returned to the control value only after one hour.

The changes in A-aD, V_D/V_T , and the nitrogen concentration difference after carbachol inspiration are shown in Figure 2 with, for comparison, the changes in the control subjects described above. The significance of the changes after carbachol inspiration has been determined by comparing the mean change at each time interval with the mean change observed in the control group of subjects at a comparable time.

There was an increase in the nitrogen concentration difference, and this remained significantly greater for 60 minutes after carbachol inspiration. The increase in A-aD occurred in all subjects and was greatest at the first measurement, 4 minutes after carbachol, thereafter decreasing progressively. The increase was significant up to minute 16. There was no change in physiological dead space, and a slight but insignificant increase in V_D/V_T . In the one subject in whom it was measured, anatomical dead space decreased by 54 ml after carbachol inspiration (Table V).

III. Effects of calcium carbonate dust

The mean results in eight subjects are presented in Table VI, and individual values for V_D/V_T and A-aD are given in Table IV. The expired volume and alveolar ventilation decreased, and there was a small fall in P_{aCO_2} and respiratory exchange ratio. Tidal volume was reduced at the first measurement after dust but soon returned to control levels. Figure 3 illustrates these changes together with the fall in alveolar oxygen

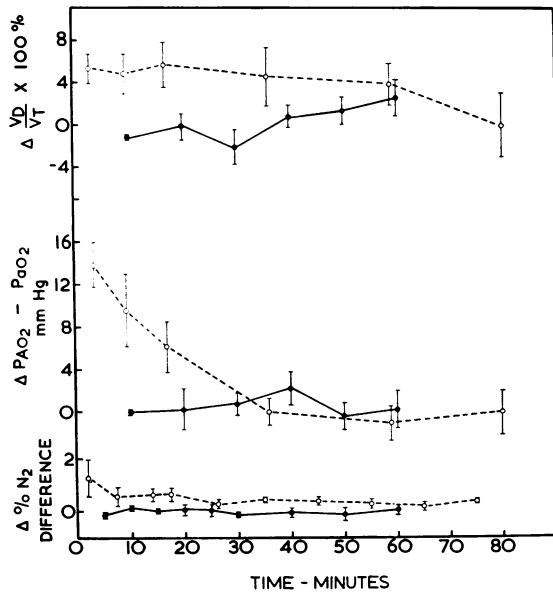


FIG. 4. CHANGES IN PHYSIOLOGICAL DEAD SPACE, ALVEOLAR-ARTERIAL DIFFERENCE IN OXYGEN TENSION, AND NITROGEN CONCENTRATION DIFFERENCE AFTER INHALATION OF CALCIUM CARBONATE DUST CLOUDS (broken lines) AND IN CONTROL SUBJECTS (continuous lines). The inhalation was completed at zero time. Mean values from eight subjects, \pm SE.

tension and the greater fall in arterial oxygen tension. The increase in A-aD is not so great as after carbachol and by 36 minutes the A-aD had regained its original value.

The changes in A-aD, V_D/V_T , and the nitrogen concentration difference are shown in Figure 4, together with the control values. The nitrogen concentration difference increased in all subjects, but the changes were somewhat variable, and the mean increase was only significant until 14 minutes after the inhalation. A-aD increased in each subject, was greatest at the first measurement, 2 minutes after breathing dust, and decreased thereafter, the increase remaining significant up to 8 minutes after breathing the dust. Physiological dead space increased in most of the subjects, but the mean changes were not significant at any time. In contrast to the subjects who breathed carbachol, V_D/V_T increased in five of the eight subjects immediately after the dust and remained elevated for an hour. In the remaining three subjects there was no change. The mean increase was significant for the first 17 minutes. Anatomical dead space was measured in three subjects (Table V), and no change was detected after breathing calcium carbonate dust.

IV. Effects of voluntary hyperventilation

a) Hyperventilation, breathing air, in sitting position. Individual values for A-aD and V_D/V_T are shown in Table VII, and the mean results are given in Table VIII. The mean expired volume

TABLE VII
Individual values for V_D/V_T and A-aD before and after hyperventilation*

Subject	V_D/V_T Time after hyperventilation (min)								A-aD Time after hyperventilation (min)							
	C1†	C2	10	20	30	45	60	C1	C2	10	20	30	45	60		
	%								mm Hg							
Hyperventilation, breathing air, sitting	1	26.7	26.5	29.4	31.5	34.9	38.4	40.1	0.9	5.3	5.6	-4.3	-1.2	-0.5	-2.2	
	2	13.1	15.6	19.7	15.8	21.6	22.3	31.3	19.3	25.6	24.4	18.4	23.5	17.4	12.5	
	3	19.0	22.5	27.3	25.4	32.9	32.0	28.0	21.8	22.4	19.9	24.8	18.4	20.6	25.4	
	4	13.9	18.6	29.8	28.0	29.8	30.5	29.9	29.2	22.2	19.7	22.5	18.3	14.9	16.1	
	5	18.5	23.8	27.6	26.0	24.2	23.0	22.3	4.4	1.7	4.0	9.5	1.0	2.0	2.0	
	6	18.3	14.9	24.7	29.9	28.3	25.2	23.1	17.3	14.9	11.1	6.5	9.8	9.1	10.9	
	7	22.4	21.0	33.2	37.2	32.3	32.4	32.5	25.0	24.9	27.4	36.0	29.0	30.0	32.3	
	8	34.2	31.1	39.0	40.3	40.3	35.6	38.5	18.7	21.4	18.0	14.6	25.4	14.6	13.3	
	9	19.9	27.5	25.0	22.5	26.5	27.4	27.7	12.0	5.6	4.0	3.0	5.0	2.0	3.0	
Hyperventilation, breathing 3 to 5% CO ₂ , sitting	10	25.4	27.4	26.2	27.8	27.1	25.6	23.4	14.0	15.7	17.0	17.0	12.0	15.0	20.0	
	11	35.8	35.8	26.1	29.9	27.8	35.5	32.8	8.0	8.7	9.0	7.0	14.9	3.0	8.8	
	12	37.8	39.4	38.6	39.1	44.1	42.0	39.0	16.5	15.8	16.6	12.4	5.4		11.1	
	13	16.2	23.0	13.3	15.0	16.0	17.5	13.2	8.8	13.0	15.6	15.5		13.0	6.0	
Hyperventilation, breathing air, supine	14	24.1	19.6	28.2	31.1	30.8	24.1	24.6	25.1	23.2	16.6	25.3	21.9	22.0	21.3	
	15	31.8	29.5	29.5	28.1	28.6	32.7	30.3	3.6	-0.8	1.3	-3.7	0.1	-1.9	1.9	
	16	19.7	26.2	39.8	27.1	25.6	27.5	26.5	7.2	5.4	9.0	3.9	5.6	1.9	3.7	
	17	24.5	24.5	30.1	26.1	25.8	21.7	23.9	1.9	2.5	3.6	6.5	4.2	10.2	11.1	

* Abbreviations as in Table I.
† C1 and C2, first and second control observations.

TABLE VIII
 Mean values in nine subjects before and after hyperventilation, breathing air, in sitting position*

Time†	PA _O ₂	Pa _O ₂	A-aD	Pa _{CO} ₂	R _E	V _D physiol. BTPS	V _T BTPS	V _D /V _T	\dot{V}_A BTPS	N ₂ difference
min	mm Hg	mm Hg	mm Hg	mm Hg		ml	ml	%	L/min	%
Control	108	91.6	16.4	35.8	0.884	141	680	20.7	7.1	
Control	106	90.0	16.0	36.6	0.866	145	641	22.4	6.6	3.4‡
10	102	87.3	14.7	37.7	0.770	167	588	28.4	5.3	
20	105	90.4	14.6	37.1	0.855	165	579	28.5	6.1	3.1
30	104	89.5	14.5	37.7	0.848	176	585	30.1	5.6	3.3
45	104	91.4	12.6	38.5	0.819	177	598	29.6	5.2	3.3
60	104	91.0	13.0	38.4	0.849	189	621	30.4	5.8	4.1
										3.6

* Abbreviations as in Table I.

† Time from end of period of hyperventilation.

‡ Mean of 3 measurements in each subject.

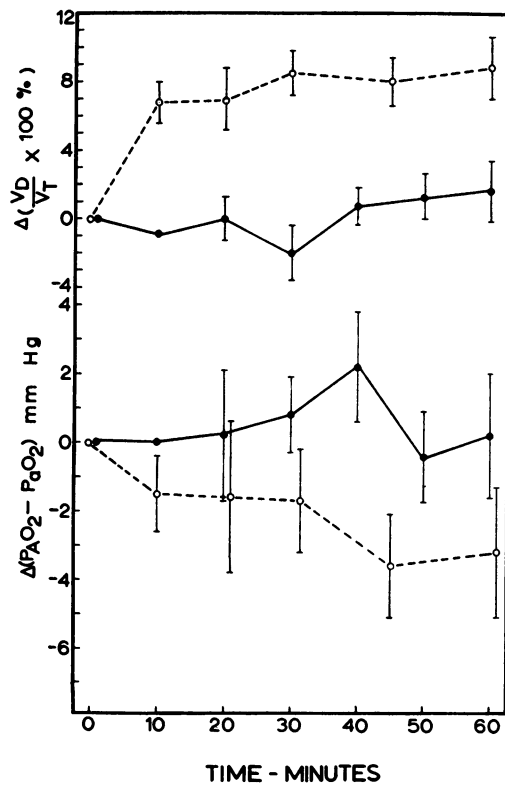


FIG. 5. CHANGE IN PHYSIOLOGICAL DEAD SPACE AND ALVEOLAR-ARTERIAL DIFFERENCE IN OXYGEN TENSION AFTER HYPERVENTILATION, IN SITTING POSTURE, BREATHING AIR. Hyperventilation ceased at zero time. Mean values \pm SE for nine subjects who hyperventilated are shown by broken line and for five control subjects by continuous line.

during the period of hyperventilation, in the seven subjects in whom it was measured, was 30.7 L per minute, and mean Pa_{CO}₂ at this time was 20.6 mm Hg (range, 15.7 to 23.6).

The mean expired volume and tidal volume were smaller after hyperventilation than before, but the decrease was no greater than that in the control subjects described in section I. Physiological dead space increased after hyperventilation and remained elevated until minute 45. In eight of the nine subjects the ratio V_D/V_T increased and remained elevated for more than 60 minutes showing no tendency to decrease. The mean value before hyperventilation was 21.6%, and from 10 to 70 minutes afterwards it ranged from 28.4 to 30.4%. The A-aD decreased in four subjects and remained unaltered in the remaining five subjects.

The changes in physiological dead space, V_D/V_T, and A-aD, from the average value before hyperventilation, were calculated for each time interval, and the mean values for the latter two indexes are shown in Figure 5. The increases in physiological dead space and V_D/V_T were significantly greater than in the control group throughout (p in each case ranging from < 0.02 to < 0.001). There was a slight decrease in A-aD, but except for the value at 45 minutes, the change was not significant. There was no alteration in the nitrogen concentration difference in the single-breath test, the mean values before

TABLE IX

Mean values in four subjects before and after hyperventilation, breathing CO₂ in air, in sitting position*

Time†	P _A O ₂	P _a O ₂	A-aD	P _a CO ₂	R _E	V _D physiol. BTPS	V _T BTPS	V _D /V _T	V̇ _A BTPS
<i>min</i>	<i>mm Hg</i>	<i>mm Hg</i>	<i>mm Hg</i>	<i>mm Hg</i>		<i>ml</i>	<i>ml</i>	<i>%</i>	<i>L/min</i>
Control	102	90.5	11.5	39.5	0.849	192	666	28.8	5.7
Control	106	92.5	13.5	37.7	0.907	183	582	31.4	5.8
10	111	96.4	14.6	35.7	0.980	184	708	26.0	7.0
20	109	96.3	12.7	36.7	0.954	200	717	27.9	7.2
30	105	93.8	11.2	37.5	0.886	198	739	28.8	6.1
45	106	96.5	9.5	38.5	1.060	199	660	30.1	6.6
60	107	95.9	11.1	36.0	0.896	157	580	27.1	5.9

* Abbreviations as in Table I.
 † Time from end of period of hyperventilation.

and after hyperventilation being 3.4 and 3.6%, respectively. Anatomical dead space was measured in four subjects and increased after hyperventilation in two, decreased in one, and did not change in the remaining subject (Table V). The mean value was 134 ml before and 143 ml after hyperventilation.

b) *Hyperventilation, breathing carbon dioxide in air, sitting.* Individual values for A-aD and V_D/V_T are given in Table VII and the mean results in Table IX. The average expired volume during hyperventilation was 22.4 L per minute, and the average P_aCO₂ was 38.8 mm Hg. The changes in V_D/V_T and A-aD after hyperventilation are illustrated in Figure 6. In neither case was the change significantly different from that in the control subjects.

c) *Hyperventilation, breathing air, supine.* Individual values for A-aD and V_D/V_T are given in Table VII and the mean results in Table X.

The average expired volume during hyperventilation was 22.7 L per minute, and the average P_aCO₂ was 23.9 mm Hg. In two subjects V_D/V_T increased after hyperventilation, but there was no change in the remaining two subjects. The mean changes in V_D/V_T and A-aD are illustrated in Figure 7; there was a significant increase (p < 0.05) in V_D/V_T 10 minutes after hyperventilation, but not at subsequent times, and A-aD remained unaltered.

d) *Effects of the infusion of angiotensin after hyperventilation.* These subjects, who hyperventilated breathing air in the sitting position received an infusion of angiotensin about 35 minutes later. In three subjects this was followed by an immediate fall in V_D/V_T to the control value before hyperventilation, and there was no rise when the infusion ceased. No change was observed in the remaining subjects, and there was no alteration in A-aD.

TABLE X

Mean values in four subjects before and after hyperventilation, breathing air, in supine position*

Time†	P _A O ₂	P _a O ₂	A-aD	P _a CO ₂	R _E	V _D physiol. BTPS	V _T BTPS	V _D /V _T	V̇ _A BTPS
<i>min</i>	<i>mm Hg</i>	<i>mm Hg</i>	<i>mm Hg</i>	<i>mm Hg</i>		<i>ml</i>	<i>ml</i>	<i>%</i>	<i>L/min</i>
Control	99.4	89.9	9.5	41.3	0.835	134	533	25.1	5.0
Control	99.0	90.6	8.4	41.5	0.822	146	584	25.0	5.9
10	89.5	81.9	7.6	41.3	0.740	148	464	31.9	3.6
20	93.6	85.7	7.9	41.7	0.752	143	509	28.1	4.4
30	99.0	91.1	7.9	40.3	0.815	154	556	27.7	5.1
45	96.6	88.6	8.0	41.1	0.800	142	535	26.5	5.1
60	99.4	89.9	9.5	40.6	0.841	165	627	26.3	6.0

* Abbreviations as in Table I.
 † Time from end of period of hyperventilation.

Discussion

In the present studies alterations in the single-breath oxygen test have been taken to indicate changes in the distribution of alveolar ventilation, and A-aD for oxygen and the physiological dead space have been used as indexes of disturbances of ventilation-perfusion ratios in the lung. It is difficult to compare values for physiological dead space in different circumstances, unless tidal volume remains constant. Physiological dead space forms a constant proportion of tidal volume over a considerable range of values for the latter, and only when tidal volume is very large does the ratio V_D/V_T decrease (12, 13). It has been assumed, therefore, that within the range of tidal volumes encountered in the present studies, a change in the ratio V_D/V_T represents a change in physiological dead space.

Effects of carbachol aerosols and dust. Alveolar ventilation was less evenly distributed after the inhalation of either a carbachol aerosol or calcium carbonate dust, and both of these agents

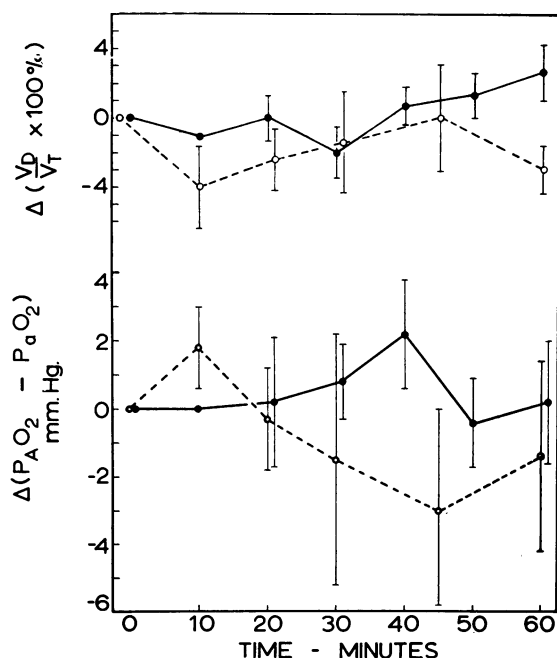


FIG. 6. CHANGE IN PHYSIOLOGICAL DEAD SPACE AND ALVEOLAR-ARTERIAL DIFFERENCE IN OXYGEN TENSION AFTER HYPERVENTILATION, IN SITTING POSITION, BREATHING AIR TO WHICH 3 TO 5% CO_2 HAD BEEN ADDED. Hyperventilation ceased at zero time. Mean values \pm SE for four subjects who hyperventilated are shown by broken line and for five control subjects by the continuous line.

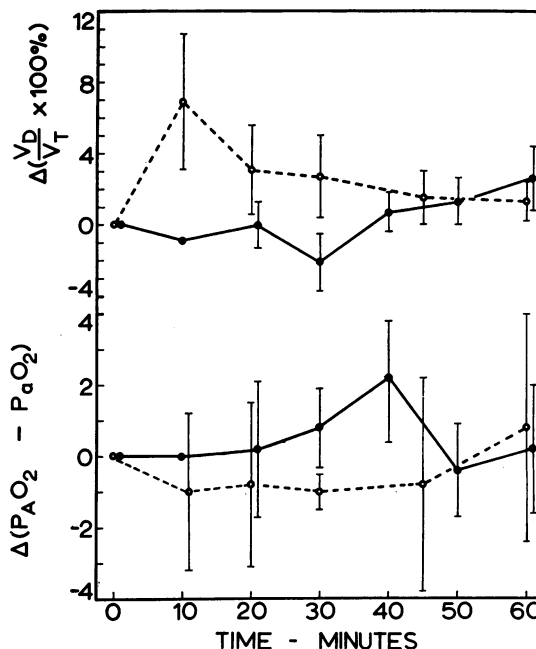


FIG. 7. CHANGE IN PHYSIOLOGICAL DEAD SPACE AND ALVEOLAR-ARTERIAL DIFFERENCE IN OXYGEN TENSION AFTER HYPERVENTILATION IN SUPINE POSITION, BREATHING AIR. Hyperventilation ceased at zero time. Mean values \pm SE for four subjects hyperventilated are shown by broken line and for five control subjects by the continuous line.

also reduced alveolar ventilation. This increased unevenness of the distribution of ventilation was accompanied by an increase of both A-aD for oxygen and V_D/V_T , although physiological dead space itself did not change. The increase was greatest within a few minutes of breathing the bronchoconstrictor materials, and both returned to normal during the subsequent hour. There was a considerable variation between individual subjects in the extent of the response to bronchoconstrictors, which is consistent with the observations of McDermott (3) concerning the changes in airway resistance.

In general, the effects of carbachol and dust were similar although the A-aD returned to normal more rapidly after dust than after carbachol. In one respect, however, the effects of the two materials differed; although V_D/V_T increased after breathing calcium carbonate dust, there was no change after carbachol inspiration. Interpretation of the change in physiological dead space would have been easier if anatomical dead space had also been measured simultaneously. The few mea-

surements made suggested that anatomical dead space decreased after carbachol, which constricts the major bronchi, but not after calcium carbonate dust. It is therefore deduced that after both carbachol and dust there was an increased frequency of high ventilation-perfusion ratios in the lungs.

Hyperventilation in the sitting position was shown to cause a prolonged increase in V_D/V_T , and the possibility was therefore considered that the changes after breathing dust or carbachol aerosol might have been the result of associated hyperventilation. The extent to which ventilation increased when breathing the bronchoconstrictor agents was certainly less than in the hyperventilation experiments, but its effect upon P_{aCO_2} was not measured. Although V_D/V_T increased after both carbachol and dust, as after hyperventilation, there was also an increase in $A-aD$ that was not seen following hyperventilation, which is therefore unlikely to have caused the changes observed after the bronchoconstrictor agents.

Of the components of the $A-aD$, that due to the effects of diffusion limitation in the lung can be neglected. It is thought to be small when breathing air, and there is no reason to believe that this changed when the bronchoconstrictor agents were administered. The increase of $A-aD$ could represent a greater blood flow through anatomical communications between the venous and arterial systems. Carbachol undoubtedly entered the systemic circulation, giving rise to flushing and in one case to a desire to micturate. It is possible that carbachol increased venous admixture through bronchial or Thebesian veins which drain into the pulmonary veins or left ventricle, or through intrapulmonary shunts. Such a mechanism, however, seems unlikely in the subjects who breathed calcium carbonate dust. The more probable explanation of the increased $A-aD$ is that ventilation-perfusion ratios in the lung were altered, so that their distribution was over a wider range. This interpretation is supported by the accompanying increase in V_D/V_T in the subjects who breathed dust, without any change in anatomical dead space.

The $A-aD$ and V_D/V_T remained increased for a shorter time than the nitrogen concentration difference in the single-breath test. Eight minutes after inhaling dust and 16 minutes after inhaling

carbachol, the distribution of ventilation-perfusion ratios had returned to normal, but this was not due to re-establishment of normal ventilation. DuBois and Dautrebande (1) reported significantly increased airway resistance up to 58 minutes and changes in compliance up to 45 minutes after inhalation of similar amounts of inert dusts. Constantine and associates (2) and McDermott (3) found that airway resistance was still markedly increased at minute 45 and 1 hour, respectively. It is possible that changes in the single-breath nitrogen test were a more sensitive index of uneven ventilation than were changes in $A-aD$ and V_D/V_T of uneven ventilation-perfusion ratios. This point is difficult to establish, but it seems unlikely, since in two subjects ventilation was sufficiently disturbed to produce changes in $A-aD$ and V_D/V_T without detectable alteration in the nitrogen concentration difference.

An alternative explanation is that a mechanism exists by which perfusion is adjusted to maintain normal ventilation-perfusion relationships throughout the lung, after an acute disturbance of the distribution of ventilation. This could result from vasoconstriction of vessels supplying poorly ventilated alveoli, which are consequently hypoxic. Although no firm conclusions can be drawn, this possibility merits further investigation, especially in subjects who breathe inert dust, in whom a direct action on the pulmonary blood vessels is unlikely.

It is not possible to state the concentration of dust which these subjects breathed, but it was comparable to that used in the studies of airway resistance (1, 2). McDermott (3) has shown that similar increases in airway resistance result from more prolonged exposure to concentrations of dust commonly encountered in certain industrial processes.

Effects of voluntary hyperventilation. The validity of measurements made after the disturbance of the steady state by hyperventilation must be considered. During the period of hyperventilation carbon dioxide was lost from the body, and after this period it was retained. Estimates of alveolar oxygen tension from the alveolar gas equation will be in error if during the period of gas collection, the volume of carbon dioxide entering the lungs from the blood is greatly different from the volume excreted in the expired gas, that

is, if P_{aCO_2} is rising or falling rapidly. Similarly, an estimate of physiological dead space is likely to be incorrect if P_{aCO_2} changes markedly during the period of measurement.

From measurements in five subjects, it was concluded that an average of 1,100 ml carbon dioxide was lost during the 3 minutes of hyperventilation. Three minutes after hyperventilation the average rate of carbon dioxide retention was about 100 ml per minute; presumably the rate of retention had been greater immediately after hyperventilation ceased. Although P_{aCO_2} remained low 2 minutes after hyperventilation, it had returned to its previous value by 10 minutes after hyperventilation. It was concluded that from 10 minutes onwards there was no appreciable retention of carbon dioxide and that a steady state had been restored. Arterial and alveolar carbon dioxide tensions had become stable, and determinations of alveolar oxygen tension and of physiological dead space after this time therefore appeared valid.

The subjects who were studied in the sitting position and breathing air showed a considerable increase in both physiological dead space and V_D/V_T after hyperventilation. Since it was also shown that anatomical dead space did not change after hyperventilation, this change indicates that the ventilation-perfusion ratio in some alveoli had increased. This increase could have resulted from a disproportionate increase in the ventilation of these alveoli or from a decrease in their perfusion. It is possible that after hyperventilation, the pattern of alveolar ventilation was altered in such a way that some alveoli became better ventilated. There is no reason to believe that this did occur, and the single-breath test provided no evidence of an alteration in the distribution of ventilation. Furthermore a change of distribution in this way, associated with an unchanged or decreased total alveolar ventilation would also lead to an increase in the A-aD for oxygen, whereas a small decrease was actually observed.

The small reduction A-aD, although statistically not significant at any one time, was consistent at each measurement after hyperventilation. It was associated with a small decrease in P_{AO_2} , which as we have previously shown (14) would be expected to lead to a decrease in A-aD. The magnitude of the change after hyperventilation

was, however, rather more than would have been predicted from the change in P_{AO_2} . The decrease in A-aD could be explained either by increased ventilation or decreased perfusion of some alveoli which before were relatively poorly ventilated; from the previous argument the latter seems the more probable.

In the normal subject in the erect position, the upper parts of the lung are both poorly perfused and relatively poorly ventilated (15), although the former is more pronounced, so that the ventilation-perfusion ratio of the upper zones is greater than the average for the whole lung. Since the changes we observed were only significant in subjects in the erect posture, it is suggested that they resulted from a decrease in blood flow to the upper parts of the lung. Since these areas have predominantly high ventilation-perfusion ratios, the effect upon physiological dead space was much more prominent than the change in A-aD.

The fall in blood flow to the upper parts of the lung presumably resulted from a fall in perfusing pressure, and the results also suggest that this effect was mediated by a change in carbon dioxide tension. It has been shown that hyperventilation in the supine position causes an increase in cardiac output (16, 17), even if a fall in P_{CO_2} is prevented (18). Burnum, Hickam, and McIntosh (19) reported a fall in systemic blood pressure due to vasodilatation, and the decrease in systemic vascular resistance was prevented by addition of carbon dioxide to the inspired gas during hyperventilation (19, 20). Nothing is known of the effects upon the pulmonary circulation, but the systemic vasodilation might lead to pooling of blood in the peripheral vessels with a consequent fall in pulmonary arterial pressure, especially in the upright position.

There remains to consider the reason for the persistence of the increase in physiological dead space for 60 minutes after hyperventilation. The effects of hyperventilation on P_{aCO_2} lasted for no more than 10 minutes, and there is no published evidence that the circulatory effects last any longer than this. It therefore appears that apical blood flow decreased because of a fall in perfusing pressure, but was not restored when that pressure returned to its former value. Such an occurrence could be explained by the closure of some blood

vessels when the pressure within them fell below a certain level and by their failure to reopen until a somewhat higher pressure was reached.

In further experiments an attempt was made to raise the pulmonary intravascular pressure by intravenous infusion of angiotensin. This is known to raise both pulmonary arterial and wedge pressure in the supine position (21), and we have some evidence that it has a similar but smaller effect in the sitting position. The results were inconclusive, perhaps in part because the magnitude of the rise in pulmonary intravascular pressures in these subjects may have been variable. The positive results are, however, consistent with the hypothesis of a critical opening pressure in the pulmonary blood vessels of the upper parts of the lung.

Summary

Aerosols of carbachol and clouds of calcium carbonate dust were administered to normal subjects, and both disturbed the evenness of alveolar ventilation as measured by the single-breath oxygen test.

After carbachol aerosol inspiration, there was an increase in alveolar-arterial difference in oxygen tension ($A-aD$), no change in the ratio of physiological dead space to tidal volume (V_D/V_T), and a decrease in anatomical dead space.

After breathing dust clouds, $A-aD$ increased and so did V_D/V_T , but there was no change in anatomical dead space.

Both $A-aD$ and physiological dead space returned to control values sooner than did the single-breath oxygen tests. The possibility that this indicates a local redistribution of pulmonary capillary blood flow in response to the acute disturbance of distribution of alveolar ventilation is discussed.

After a brief period of voluntary hyperventilation in the sitting position, there was an increase in physiological dead space and in V_D/V_T that persisted for 60 minutes but only a small and non-significant decrease in $A-aD$.

When a fall in P_{CO_2} was prevented by addition of carbon dioxide to the inspired gas during hyperventilation, there was no significant alteration in V_D/V_T or $A-aD$.

Subjects who hyperventilated, breathing air in

the supine position, showed hardly any change in V_D/V_T and no alteration in $A-aD$.

It is postulated that hypocapnia during hyperventilation may lead to a fall in pulmonary arterial pressure and a decreased blood flow to the upper zones of the lung; the possible mechanisms are discussed.

Acknowledgments

We are indebted to Mr. J. W. Skidmore of the M.R.C. Pneumoconiosis Research Unit for the measurements of particle size and to Mrs. Anne Hollyhock for her excellent technical assistance.

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ERRATUM

In the paper entitled, "On the Concentrating Defect in Cirrhosis of the Liver," by Hershel Jick, Donald E. Kamm, Julian G. Snyder, Robert S. Morrison, and Thomas C. Chalmers, published in the February issue (p. 258), the following corrections should be noted: On page 259 and in the last column of Tables III and IV, the percentage of urea per nonurea solute should read *percentage of urea per total solute excretion*. The last column of numbers in Table III, beginning with Patient 1, should be 44, 65, 55, 29, 45, 68, 20, 43, 19, 65, and 47.