The effect of intermittent positive pressure breathing and voluntary hyperventilation upon the distribution of ventilation and pulmonary blood flow to the lung in chronic obstructive lung disease.

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Research Article

The Effect of Intermittent Positive Pressure Breathing and Voluntary Hyperventilation upon the Distribution of Ventilation and Pulmonary Blood Flow to the Lung in Chronic Obstructive Lung Disease *

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Intermittent positive pressure breathing (IPPB) from an apparatus applying positive pressure to the mouth during inspiration is widely used in the treatment of obstructive lung disease. The literature has recently been well reviewed by Sheldon (1). There was early concern with its effects in decreasing cardiac output (2, 3), which are avoided by using equipment that gives a type III mask pressure curve and hence letting the positive pressure phase, i.e., inspiration, occur at a high flow rate and occupy only a small fraction of the respiratory cycle, expiration being prolonged and against zero mask pressure. This type of pressure curve is obtained with machines in current use.

There have been many therapeutic successes following the use of IPPB in severe respiratory failure (1). Its value, however, is debated by some. For example, Sukumalchantra, Park, and Williams maintain that in patients in acute ventilatory failure it frequently fails to lower the arterial carbon dioxide tension (4). Most authors maintain that it is only useful, or is more useful, when given with bronchodilators (5–7). Some maintain that it is not only useless (5, 7) but actually harmful (5) to administer oxygen by this method, in that arterial CO_2 rises during such treatment. Most workers, however, have found that arterial CO_2 falls during IPPB both when air (8) or O_2 (9) is given.

In reviewing this literature, one is impressed by the fact that most authors, in an effort to obtain the maximal therapeutic effect on blood gases, used a variety of agents in addition to IPPB, such as O_2, bronchodilators, wetting agents, and antibiotics (10, 11). Furthermore, the tests were performed in patients with widely different degrees of incapacity and with varying relations to the time of application of IPPB, some tests being done immediately after a single treatment (7), others after a course of treatments lasting several weeks (10). Two studies in recent years added greatly to our knowledge of the mechanism by which it produces its effects. Torres, Lyons, and Emerson (12) have found that the least ventilated spaces in the lungs are better ventilated during IPPB. Cohen, Hemingway, and Hemingway (13) have demonstrated conclusively that IPPB has more effect in increasing ventilation and improving its distribution when administered with isoproterenol. However, there seems to be no study in which changes in ventilation and its distribution have been quantitatively related to changes in blood gases and in ventilation-perfusion ($\dot{V}_A/\dot{Q}_c$) ratios.

In the present study, an effort has been made to simplify some of the issues involved and to present a coordinated assessment of changes in both ventilation and blood gases. It is concerned only with the various interrelated physiological phenomena that occur in emphysematous patients during 15- to 20-minute periods of IPPB, not with long term effects. The physiological entities with which we are concerned are *1*) total ventilation, *2*) distribution of ventilation, *3*) distribution of perfusion and of $\dot{V}_A/\dot{Q}_c$ ratios, *4*)

oxygen consumption of the body, and *5*) the effects of these on arterial blood gases. Separate studies were made with air and O_2 as the inspired gas. The effects of IPPB were compared with the resting state and with voluntary hyperventilation (VH) as control situations. Accessory factors such as bronchodilators were excluded in order to assess the effects of IPPB alone.

Methods

Selection of patients. The subjects were patients with chronic respiratory insufficiency recovering from a superimposed episode of acute respiratory failure that had caused their admission to the hospital. They were selected for study because they were well enough to walk or be brought in a wheelchair to the laboratory, unusually cooperative, and most likely to persist in training in VH, which few severely disabled patients are able to maintain for 16 minutes. They presented clinical and radiological evidence of severe chronic pulmonary emphysema, chronic bronchitis, or both, and were receiving regular treatment consisting of IPPB, bronchodilators, and in some patients, antibiotics. Three (A.F., W.W., and M.O.) were receiving digitalis for treatment of cor pulmonale. All had had routine lung function studies including lung volume determination and arterial blood gas analysis, which had shown arterial oxygen unsaturation and carbon dioxide retention during the preceding acute episode. W.W. had a higher maximal breathing capacity than the other patients. He was a bronchitic, with heart failure due to cor pulmonale during acute exacerbations of bronchitis. His chest X rays and Gough section of lung at autopsy have been published, as have X-ray findings on A.F. (14).

Procedure. Patients were previously rehearsed to familiarize them with the equipment and train them in the procedures, especially in VH. Six studies were carried out on most patients while they were breathing ambient air and O_2 administered in each of three states: at rest, during IPPB, and during VH. During ambient air breathing the minute ventilation ($\dot{V}E$), arterial O_2 saturation (Sa), and arterial CO_2 tension (Pa_{CO_2}) were measured in each of the three states. During O_2 breathing minute ventilation, the nitrogen washout curve, and the arterial blood gases were measured in each state. Arterial blood samples were taken in all patients at the end of 15 to 20 minutes just before the end of the study. The studies on each subject occupied two or three mornings. They were done in the sitting position with back supported.

Between studies, a resting period of 1 hour permitted the return of the blood gases to the resting state during air breathing. This was confirmed by drawing a sample of arterial blood for analysis before starting the next study. The order used in the present description was not necessarily followed. However, studies during IPPB always preceded studies during VH. The same sheet of paper was used on the recording Tissot spirometer, and during the latter study patients were urged to match their ventilation

against the record of the previous IPPB study. The Bird respirator was used without bronchodilators and with an inspiratory pressure of 12 cm H_2O in the IPPB studies.

It was impractical in most studies for the subject to be in a steady state of IPPB or VH before being switched to O_2 breathing for measurement of the functional residual capacity and N_2 washout in the same ventilatory state. In the studies recorded in Tables II and III VH or IPPB began at the same breath as did O_2 breathing. These are designated 15-minute studies. However, in studies performed on four patients, recorded in Table IV and designated 30-minute studies, the subjects were switched to breathing O_2 for 15 minutes after they had reached a steady state while breathing air for 15 minutes. This necessitated the use of two IPPB machines, one for air and one for oxygen.

Arterial blood gases were analyzed by the Van Slyke method and expired O_2 and CO_2 during air breathing by the Scholander method. The N_2 washout curve was followed by the "two-balloon" procedure, the expired volume and the N_2 concentration being measured in $\frac{1}{2}$-minute collections of mixed expired air during a 15-minute or longer period of O_2 breathing (15). Allowance is made for N_2 eliminated from tissues each $\frac{1}{2}$ minute. This method eliminates the uncertainties and assumptions inherent in the interpretation of end tidal gas samples. It permits assessment of the total quantity of N_2 that would be eliminated from the lungs, excluding tissue N_2, in an infinitely long period of O_2 breathing and gives values for the functional residual capacity (L_T) comparable to those obtained with the body plethysmograph (16). It also gives the most reliable assessment of that quantity of N_2 which is very slowly eliminated during O_2 breathing in obstructive disease of the lungs. It thus delineates the behavior of the slow space, a term coined by Hickam, Blair, and Frayser (17) to refer to a group of very poorly ventilated alveoli or other lung spaces that dominate the behavior of such lungs. Though such spaces are probably scattered throughout both lungs, the singular word "space" is used because they behave as one unit, apparently all having the same ventilation per unit volume (18–21). From the two-balloon N_2 washout technique, it is possible to make reliable estimates of the volume (L_3) and the alveolar ventilation ($\dot{V}A_3$) and of the turnover rate ($\dot{V}A_3/L_3$) in the slow space (15). When arterial O_2 saturation, total O_2 consumption, total ventilation, and the volume and ventilation of the slow space are known, then *1*) the fractional perfusion of the slow space (i.e., the maximal fraction of the cardiac output that may perfuse the slow space and be compatible with the observed saturation), and *2*) the minimal value of its ventilation-perfusion ratio ($\dot{V}A_3/\dot{Q}c_3$) can be determined from the logarithmic graph previously published (22).

The symbols used here are based on those in general use with minor modifications: L refers to alveolar volume plus dead space or to subdivisions of this in variously ventilated spaces. L_T is the functional residual capacity (FRC). The three subscripts 1–2, 3, and T refer, respectively, to collective values in fast spaces, to those in the slow space, and to the total value in all spaces (22).

Results

15-minute studies with arterial blood gases

Ten patients were studied, and the results are given in Tables I, II, and III. Two sets of averages are given. One, referred to subsequently in the text, is the average of all measurements on all subjects including results in those who were not studied in all three states; the other is the average in the five patients in whom all studies were successfully performed. These means, depicted in Figures 1, 2, and 3, have the advantage of presenting and pictorially illustrating more complete studies on fewer patients. Both sets of mean values show the same trends.

a) *Ambient air breathing (Table II)*. Ten patients were studied at rest and during IPPB and eight during voluntary hyperventilation.

Minute ventilation averaged 10.55 L per minute (range, 8.35 to 13.50) at rest, 17.86 L per minute (range, 12.54 to 25.33) during IPPB, and 15.80 L per minute (range, 11.1 to 24.9) during VH. Thus, these patients were hyperventilating even at rest. Two of these patients (O.N. and R.A.) were able to surpass by voluntary effort for 15 minutes the ventilation achieved during IPPB. Two others (A.F. and J.C.), despite preliminary training, were unable to sustain an adequate degree of VH for more than a few minutes and so had to be excluded from these studies. In one of these two, A.F., the ventilation achieved during IPPB (14.1 L per minute, Table II) was close to his maximal breathing capacity of 16 L per minute, and it is therefore not surprising that he was unable, without mechanical aid, to match this performance for 15 minutes.

Oxygen consumption (V_{O_2}) averaged 249 ml per minute (range, 199 to 296) at rest, 261 ml per minute (range, 219 to 344) after about 15 minutes of IPPB, and 302 ml per minute (range, 248 to 353) after 15 minutes of VH.

Respiratory quotient averaged 0.88 (range, 0.83 to 0.93) at rest, 0.96 (range, 0.85 to 1.12) after about 15 minutes on IPPB, and 0.94 (range, 8.99 to 1.10) on VH.

Arterial O_2 saturation averaged 89% (range, 86 to 91%) at rest; on IPPB and VH it rose to mean values of 95% and 96%, respectively, i.e., the abnormality in the resting saturation is correctable by VH as well as by IPPB.

Arterial CO_2 tension (Pa_{CO_2}) averaged 47 mm Hg (range, 40 to 53) at rest, and it fell to the subnormal mean value of 35 mm Hg both on IPPB and VH.

The oxygen cost of the extra ventilation ($\Delta V_{O_2}/\Delta V_E$) is the ratio between additional O_2 consumption above the resting value and the additional ventilation. It averaged 2.2 ml O_2 and 10.7 ml O_2 per L ventilation on IPPB and VH, respectively.

b) *Oxygen breathing: N_2 washout studies (Table III)*. These were carried out on nine patients at rest, eight during IPPB, and six during VH.

Minute ventilation averaged 9.8 L per minute (range, 7.8 to 10.9) at rest, 14.6 L per minute (range, 12.5 to 21.2) during IPPB, and 14.0 L per minute (range, 10.6 to 18.4) during VH. These values were on the whole less than those during air breathing.

TABLE I

Physical characteristics, bellows function, and lung volumes

Patient	Age	Body surface area	Maximal breathing capacity	Vital capacity	Residual volume/ total lung capacity	Total lung capacity	Residual volume
	years	*m²*	*L/min*	*L*	*%*	*L*	*L*
J.F.	48	1.65	32	1.7	68	4.3	2.9
A.F.	57	1.35	16	2.2	70	8.5	6.0
L.L.	52	1.59	19	1.1	55	3.8	2.1
J.C.	65	1.46	28	2.5	64	6.9	4.4
W.W.	63	1.89	54	3.7	54	6.9	3.7
H.V.	46	1.75	23	2.5	58	6.4	3.7
N.R.	54	1.70	37	2.8	58	6.9	4.0
M.O.	65	1.90	29	2.7	52	6.4	3.3
R.A.	60	1.80	34	2.2	68	7.3	5.0
O.N.	68	1.55	35				
Mean	58	1.66	31	2.4	61	6.4	3.9

TABLE II

*15-minute studies: air breathing**

Patient	Condition	$\dot{V}_E$	f	$\dot{V}_{AT}$	$\dot{V}_{O_2}$	Sa	Pa_{CO_2}	$\Delta\dot{V}_{O_2}/\Delta\dot{V}_E$
		L/min		*L/min*	*ml/min*	*%*	*mm Hg*	*ml/L*
J.F.	R	8.8	14	6.0	293	89	53	
	IPPB	15.8	16	12.6	290	95	37	−0.4
	VH	13.9	16	10.7	319	95	46	+5.1
A.F.	R	9.2	20	5.2	199	91	53	
	IPPB	14.1	16	10.9	219	97	38	+4.1
	VH							
L.L.	R	9.9	19	6.1	217	90	49	
	IPPB	13.4	16	10.2	221	94	42	+1.1
	VH	11.1	17	7.7	248			+25.8
J.C.	R	12.2	24	7.4	218	86	47	
	IPPB	16.2	16	13.0	227	89	44	+2.3
	VH							
W.W.	R	11.2	22	6.8	266	93	43	
	IPPB	25.3	16	22.1	293	96	26	+1.9
	VH	16.8	16	13.6	298	96	27	+5.7
H.V.	R	8.4	14	5.5	280	81	54	
	IPPB	12.5	12	10.1	344	98	40	+15.3
	VH	11.4	14	8.6	329	97	42	+16.0
N.R.	R	13.4	24	7.6	251	90	41	
	IPPB	24.0	18	20.4	266	95	28	+1.2
	VH	18.0	22	13.6	296	94	31	+8.0
M.O.	R	8.9	16	5.7	242	92	44	
	IPPB	19.0	15	16.0	226	93	30	−1.6
	VH	15.1	18	11.5	316	94	36	+11.9
R.A.	R	10.0	18	6.4	296	91	40	
	IPPB	13.8	12	11.4	287	96	34	−2.4
	VH	15.2	14	12.4	353	96	32	+11.0
O.N.	R	13.5	24	8.7	228	88	42	
	IPPB	24.4	16	21.2	232	99	28	+0.4
	VH	24.9	24	20.1	255	97	32	+2.37
Mean of all	R	10.6	20	6.5	249	89	47	
	IPPB	17.9	15	14.8	261	95	35	+2.2
	VH	15.8	18	12.3	302	96	35	+10.7
Mean of J.F.,	R	10.1	18	6.5	277	89	46	
W.W., H.V.,	IPPB	18.3	15	15.3	296	96	33	+3.1
N.R., R.A.	VH	15.0	16	11.8	319	96	36	+9.2

* Abbreviations: $\dot{V}_E$ = minute ventilation; f = respiratory rate; $\dot{V}_{AT}$ = total alveolar ventilation; $\dot{V}_{O_2}$ = oxygen consumption; Sa = arterial O_2 saturation; Pa_{CO_2} = arterial CO_2 tension; $\Delta\dot{V}_{O_2}/\Delta\dot{V}_E$ = extra O_2 consumption per liter of extra ventilation; R = respiratory quotient; IPPB = intermittent positive pressure breathing; and VH = voluntary hyperventilation.

The arterial O_2 saturation rose during O_2 breathing to 100% in all patients. Values over 100% in Table III reflect an O_2 content in excess of the O_2 capacity of hemoglobin, due to dissolved O_2.

Arterial CO_2 tension was 1 mm Hg higher (mean, 48 mm Hg) than when breathing air. This change was compatible with the lower minute ventilation while breathing O_2. It fell during IPPB and VH, breathing O_2, to subnormal levels.

The functional residual capacity averaged 5.5 L at rest and 5.4 and 5.3 L when measured during IPPB and VH, respectively. The volume measured by N_2 washout is the gas volume in the lungs at the moment when the patient is switched to O_2 breathing, which is the moment when IPPB or VH begins, both in this and in other studies

(12, 13). In studies where comparable changes in ventilation have occurred, e.g., during exercise, the values measured with the N_2 washout beginning after 7 minutes of hyperventilation were less than 10% greater than those at rest (23–25). To ascertain how much L_T changes during IPPB, we performed the 30-minute studies described later.

The turnover rate of the slow space (V_{A3}/L_3) is the alveolar ventilation in liters per minute per liter of slow space. At rest it averaged 0.200 minute^{-1} (range, 0.117 to 0.450), and it increased during IPPB to average 0.316 minute^{-1} (range, 0.140 to 0.880). During VH there was a lesser increase to a mean of 0.245 minute^{-1} (range, 0.258 to 0.364). The turnover rates of the fast

spaces are high, ranging from 1.4 to 7.4 minutes^{-1} at rest and more during VH and IPPB. This is about 10 to 40 times greater than the turnover rate in the slow space. Since there is inhomogeneity within the fast spaces, this factor, large as it is, underestimates the high degree of inhomogeneity in these emphysematous lungs.

The alveolar ventilation of the slow space (V_{A3}) averaged 721 ml per minute (range, 394 to 1,620) at rest. It increased in all but two individuals, L.L. and J.C., during IPPB to a mean of 1,104 ml per minute (range, 399 to 3,170). During VH it was virtually unchanged from the resting value, averaging 710 ml per minute (range, 276 to 1,260). The alveolar ventilation of the slow space expressed as a percentage of

TABLE III

15-minute studies: measurements made during oxygen breathing and entities derived from them*

Subject	Condition	$\dot{V}_E$	f	Sa	Pa$_{CO_2}$	$\dot{V}_{AT}$	$\dot{V}_{A3}$	$\dot{V}_{A3}/L_3$	L_T	L_3	L_3/L_T	$\dot{V}_{A3}/\dot{Q}_{C3}$	$\dot{Q}_{C3}/\dot{Q}_{CT}$	$\dfrac{\dot{Q}_{C3}}{\dot{Q}_{CT}} \div \dfrac{L_3}{L_T}$
		L/min		*%*	*mm Hg*	*L/min*	*ml/min*	*ml/L*	*L*	*L*	*%*		*%*	*%*
J.F.	R	9.7	25	105	58	4.7	394	130	4.6	3.0	65	0.160	42	65
	IPPB	12.5	12	106	47	10.1	813	324	4.4	2.5	57	0.333	42	74
	VH	12.2	22			7.8	341	158	4.5	2.2	48	0.222	24	50
A.F.	R	9.7	21	106	49	5.5	582	167	6.8	3.5	52	0.270	54	104
	IPPB	14.0	13			11.4	770	245	6.9	3.1	46	0.475	37	80
	VH													
L.L.	R	8.1	24	102	56	3.3	448	117	5.0	3.8	76	0.225	46	61
	IPPB	13.1	22			8.7	399	140	4.2	2.9	65	0.250	36	55
	VH													
J.C.	R	9.9	24	105	53	5.1	794	166	5.7	4.8	24	0.268	68	81
	IPPB	12.6	27			7.2	676	180	5.7	3.8	66	0.266	56	85
	VH													
W.W.	R	10.4	20	104	38	6.5	1,620	450	4.3	3.6	85	0.400	75	88
	IPPB	17.5	14	108	27	14.7	3,170	880	4.3	3.6	84	0.620	86	102
	VH	13.9	16			10.7	1,260	364	4.3	3.5	81	0.431	49	60
H.V.	R	7.8	12	105	49	5.4	762	205	5.3	3.7	70	0.209	65	93
	IPPB	12.6	12			10.2	1,040	223	5.7	4.7	82	0.658	23	28
	VH	10.9	14			8.1	1,020	297	5.8	3.4	58	0.531	34	59
N.R.	R	10.9	22	109	35	6.8	536	217	4.8	2.4	51	0.222	48	94
	IPPB	21.2	16		28	18.0	644	224	5.3	2.8	54	0.311	39	72
	VH	17.7	22	106	30	13.8	276	179	5.0	1.5	31	0.172	27	87
M.O.	R	10.9	18	104	42	7.4	452	133	6.7	3.3	51	0.233	40	78
	IPPB													
	VH	18.4	20	102	26	14.4	645	197	6.9	3.2	47	0.369	38	81
R.A.	R	11.0	24			6.2	897	219	6.7	4.1	61	0.275	55	90
	IPPB	13.2	12	106	32	10.8	1,320	310	6.7	4.3	63	0.450	51	81
	VH	10.6	12			8.3	719	277	5.4	2.5	48	0.351	29	60
Mean of all	R	9.8	21	105	48	5.7	721	200	5.5	3.6	66	0.251	55	84
	IPPB	14.6	16	107	34	11.4	1,104	316	5.4	3.5	65	0.420	46	72
	VH	14.0	18	104	28	10.4	710	245	5.3	2.7	52	0.346	34	66
Mean of J.F.,	R	10.0	21	106	45	5.8	842	244	5.1	3.4	66	0.253	57	86
W.W., H.V.,	IPPB	15.4	13	107	33	12.7	1,397	392	5.3	3.6	68	0.474	48	71
N.R., R.A.	VH	13.1	17	106	30	9.6	723	255	5.0	2.6	53	0.341	32	63

* Abbreviations: $\dot{V}_{A3}$ = alveolar ventilation of slow space; $\dot{V}_{A3}/L_3$ = turnover rate; L_T = functional residual capacity; L_3 = slow space; L_3/L_T = fraction of lung volume in slow space; $\dot{V}_{A3}/\dot{Q}_{C3}$ = ventilation-perfusion ratio in slow space; $\dot{Q}_{C3}/\dot{Q}_{CT}$ = percentage of cardiac output perfusing slow space; and $\dot{Q}_{C3}/\dot{Q}_{CT} \div L_3/L_T$ = index of perfusion of slow space.
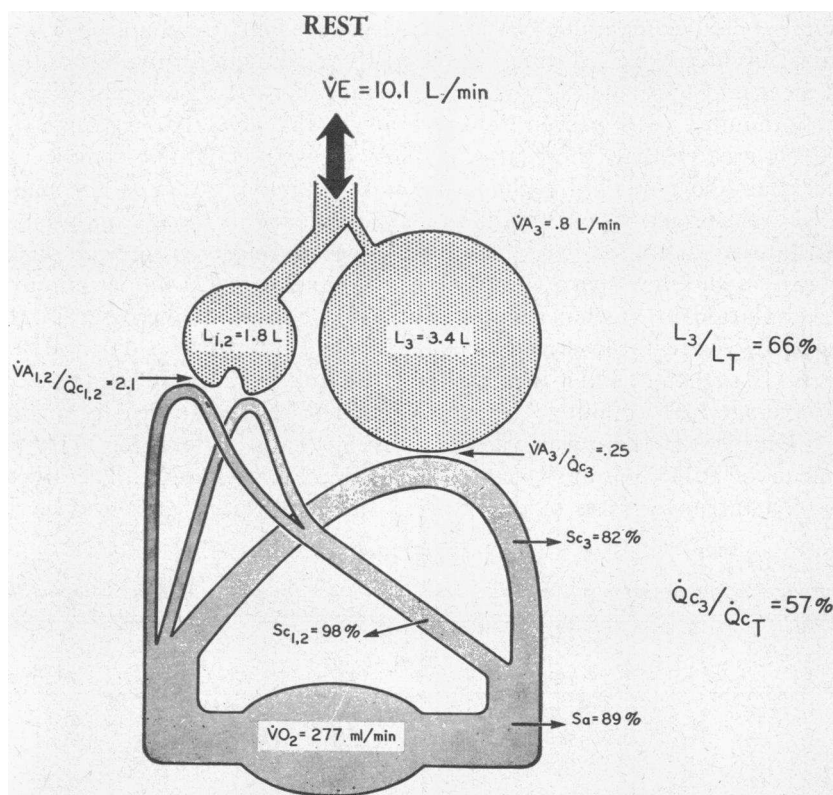
FIG. 1. DIAGRAM OF DISTRIBUTION OF VENTILATION AND PERFUSION AT REST. Figures 1, 2, and 3 give mean values of five subjects able to complete all studies during voluntary hyperventilation (VH) and intermittent positive pressure breathing (IPPB). The data for minute ventilation ($\dot{V}E$) and arterial oxygen saturation (Sa) were determined during air breathing, and those for the volume (L_3) and ventilation ($\dot{V}A_3$) of the slow space were determined during 100% oxygen breathing. Ventilation and blood flow per minute are indicated by the diameter of the airways and blood vessels and lung volumes by the diameter of the lung spaces. At rest the alveolar ventilation of the slow space is 0.8 L per minute or 8% of the minute ventilation. Its volume is 66% of the functional residual capacity (FRC), and its blood flow is 57% of the cardiac output. Symbols are as in the text.

total minute ventilation averaged 7.4% at rest, 7.5% of the increased minute ventilation during IPPB, and only 5.1% of the comparable minute ventilation during voluntary hyperventilation. The alveolar ventilation of the fast spaces of these patients constitutes the remainder of the total alveolar ventilation.

The volume of the slow space (L_3) at rest averaged 3.6 L (range, 2.4 to 4.8) constituting, on the average, 66% of L_T. It either increased or decreased on IPPB, averaging 3.5 L (range, 2.5 to 4.7) and constituted 65% of L_T. In VH there was a consistent tendency for L_3 to be reduced to a mean of 2.7 L (range, 1.50 to 3.5), constituting a smaller percentage (52%) of L_T.

The ventilation-perfusion ratio of the slow space ($\dot{V}A_3/\dot{Q}c_3$) is the minimal value compatible with the data. It averaged 0.25 (range, 0.16 to 0.4) at rest, 0.42 (range, 0.25 to 0.66) during IPPB, and 0.35 (range, 0.17 to 0.43) during VH. The $\dot{V}A/\dot{Q}c$ of the fast spaces as a group averaged 2.37 (range, 1.21 to 3.66) and rose to even higher values during IPPB and VH. A ratio of 1.0 is sufficient to almost fully saturate the blood, i.e., to 97 or 98%.

The fraction of cardiac output perfusing the slow space ($\dot{Q}c_3/\dot{Q}c_T$) is the maximal value compatible with the data. It averaged 0.55 at rest (range, 0.42 to 0.75), 0.46 (range, 0.23 to 0.86) during IPPB, and during VH it fell to 0.34 (range,

0.24 to 0.49). These three means for the upper limit of $\dot{Q}c_3/\dot{Q}c_T$ during rest, IPPB, and VH are, respectively, 0.57, 0.48, and 0.32, if we consider the data of only those five patients who were studied under all three conditions.

If the lung were evenly perfused in relation to the volume of the slow space, then $\dot{Q}c_3/\dot{Q}c_T$ should be equal to the fractional volume, L_3/L_T. For instance, the slow space that constitutes 66% of the FRC at rest would be perfused by 66% of the cardiac output. However, if this were the case application of the method of analysis previously developed (22) and used here shows that the arterial O_2 saturation could not be as high as the observed value (mean, 89%) and would instead have to be about 82%.

In the sense that 66% of the lung is perfused by only 55% of the cardiac output at rest, the slow space, though overperfused in relation to its ventilation, is underperfused in relation to its volume. The index of perfusion of the slow space relative to its volume $(\dot{Q}c_3/\dot{Q}c_T)/(L_3/L_T)$

had a mean value of 0.84 at rest, 0.72 during IPPB, and 0.66 in VH.

25-minute studies of FRC and distribution of ventilation

The preceding section reports the effects of VH and IPPB on arterial blood gases and other entities in studies lasting 15 to 20 minutes, breathing air or O_2. However, in other studies designed to assess changes in L_T in IPPB and VH four different but comparable patients hyperventilated air or breathed air from an IPPB machine before being switched to hyperventilating O_2 or breathing O_2 from a second IPPB machine. Thus, in these studies the patients continuously hyperventilated or were on IPPB without interruption for 30 minutes, during which the inspired gas was changed from air to O_2. We are not aware of any previous studies of this type designed to show how much L_T, as measured by prolonged N_2 washout in emphysema, changes during IPPB.
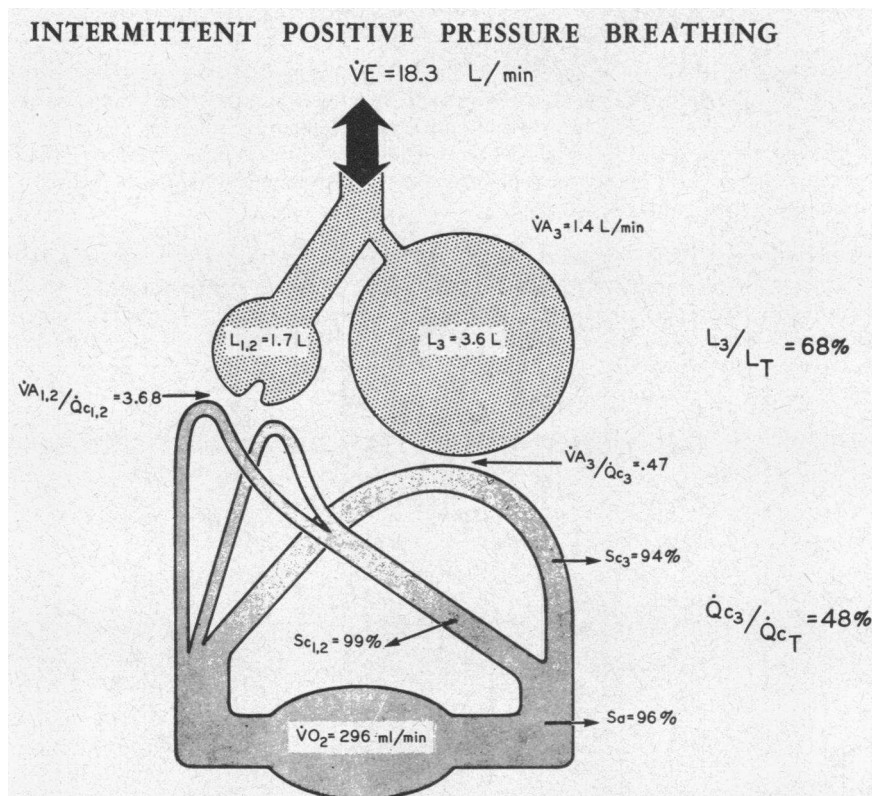

FIG. 2. DISTRIBUTION OF VENTILATION AND PERFUSION DURING IPPB. $\dot{V}A_3$ has risen to 1.4 L per minute, which is 8% of the minute ventilation. L_3 is 68% of the FRC. Its blood flow has decreased to 48% of the cardiac output. Symbols are as in the text.
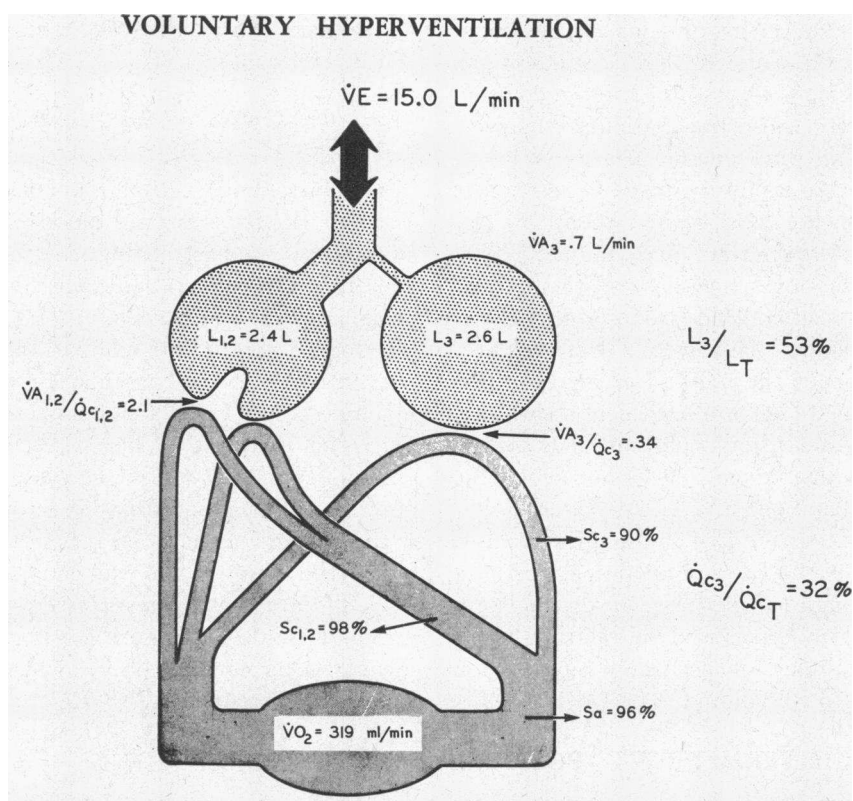
FIG. 3. DISTRIBUTION OF VENTILATION AND PERFUSION DURING VOLUNTARY HYPER-
VENTILATION. $\dot{V}_{A_3}$ is 0.7 L per minute or 5% of the minute ventilation. L_3 is 2.6 L,
which corresponds to 53% of the FRC. It is lower than the volume of the slow space
at rest by 0.8 L. The blood flow to this space has further decreased to 32% of the cardiac
output. Symbols are as in the text.

TABLE IV

*25-minute studies of changes in FRC and in distribution of ventilation**

Subject	Condition	$\dot{V}_E$	f	$\dot{V}_{A_T}$	$\dot{V}_{A_3}$	L_T	L_3	L_3/L_T
		L/min		*L/min*	*ml/min*	*L*	*L*	*%*
A.S.	R	8.9	23	5.3	460	4.2	2.6	61
	IPPB							
	VH	20.6	28	16.2	568	4.4	1.8	40
J.G.	R	10.0	20	7.6	1,430	8.4	7.6	92
	IPPB	12.5	16	10.6	1,473	8.4	7.3	87
	VH	14.3	32	10.3	1,639	9.3	7.9	85
J.C.	R	11.6	18	9.1	972	4.8	2.9	59
	IPPB	14.1	13	12.3	1,900	5.6	4.3	76
	VH							
E.P.	R	8.3	20	6.2	342	4.8	2.7	67
	IPPB	12.7	20	10.6	380	4.9	2.7	55
	VH	8.6	26	6.0	528	4.5	3.2	72
Mean values	R	10.0	19	7.6	914	6.0	4.4	69
of paired	IPPB	13.1	16	11.2	1,251	6.3	4.8	73
studies								
	R	9.0	21	6.4	744	5.8	4.3	70
	VH	14.5	29	10.8	911	6.1	4.3	66

* FRC = functional residual capacity.

As shown in Table IV, L_T increased on the average of 0.31 L during IPPB and by 0.30 L during VH. The ventilation of the slow space ($\dot{V}_{A3}$) increased by 0.37 L during IPPB and by 0.167 L during VH. The volume of the slow space (L_3) increased by 0.341 L during IPPB and decreased by 0.112 L during VH.

It is significant that the changes in L_T, L_3, and $\dot{V}_{A3}$ between rest and VH and between rest and IPPB are generally of the same order of magnitude as those already presented, although there is a tendency for the lungs to inflate by a few hundred milliliters during sustained VH or IPPB.

Discussion

Results during air breathing

Effect on blood gases. Both IPPB and VH restored the low resting (89%) arterial O_2 saturation to a nearly normal mean value (95 or 96%). Both procedures reduced the high resting Pa_{CO_2} (47 mm Hg) to a low value (35 mm Hg). This change was accomplished in 15 minutes with each procedure while breathing air and without bronchodilators. This considerable reduction in Pa_{CO_2} coincided with only a small rise from 0.88 to 0.96 or 0.94 in the respiratory quotient (R) measured by gas collections at the end of the 15-minute period. The smallness of the rise in R at this time suggests that after 15 minutes these subjects were approaching a steady state. Presumably, R was higher in the earlier minutes of hyperventilation. The effects of IPPB on the blood gases are greater than some of those published by others where there was, on the whole, a smaller minute ventilation during IPPB (3, 8). On the other hand, the average Pco_2 in our study, 35 mm Hg, was less affected by IPPB with a mean ventilation of 17 L per minute than it was in the patients of Cohen and associates (13). Their average Pco_2 fell to 29.9 mm Hg during IPPB with a larger minute ventilation, 22 L per minute administered with isoproterenol. Thus the changes in blood gases reported by different investigators are related to the minute ventilation achieved by their patients.

The work of breathing. These subjects were trained to hyperventilate at three or four previous sessions. An effort was made to match their ventilation during VH and IPPB by warning them sometimes to breath less during IPPB, which was always performed first, and urging them to breath more if necessary during VH when this was performed later.

Despite the training several subjects, most of them not described here, were unwilling or unable to voluntarily hyperventilate to an adequate degree for 15 minutes. For this reason some studies had to be abandoned during their performance or discarded later because an adequate increase in ventilation was not achieved.

The measurements of oxygen consumption confirm that VH entails a considerable effort by these patients. The average increase in $\dot{V}o_2$ above the resting level was 53 ml per minute during VH and only 12 ml per minute during IPPB where, on the average, a higher ventilation was achieved. The oxygen cost of the extra ventilation, $\Delta\dot{V}o_2/\Delta\dot{V}E$, averaged 2.2 ml per L during IPPB and 10.7 ml per L during VH. The latter is in good agreement with other data on voluntary hyperventilation in emphysema. For example, recalculation of the data of Fritts, Filler, Fishman, and Cournand (26) shows their average value of $\Delta\dot{V}o_2/\Delta\dot{V}E$ in emphysematous patients during VH was 11.2 ml per L. Thus, during IPPB the machine, or rather the potential energy of the compressed gas in the tank, does about three-fourths of the mechanical work necessitated by the extra ventilation. This is the most important advantage of IPPB over VH as performed here. It enables patients with obstructive disease to remain in a nearly resting state while hyperventilating (27).

Another aspect of oxygen consumption deserves mention. When $\dot{V}A/\dot{Q}c$ ratios are low, as they are in the slow space in emphysema, then mixed venous saturation has, as shown in Figure 3 of a previous publication (28), a significant influence on end capillary saturation not seen in normal men. Any increase in $\dot{V}o_2$ is associated either with a fall in mixed venous saturation or with an increase in cardiac output associated with a decrease in $\dot{V}A/\dot{Q}c$ ratios. It therefore tends to lower arterial O_2 saturation in emphysema (22). The greater increase in $\dot{V}o_2$ during VH tends to reduce its effectiveness in raising O_2 saturation. The fact that it is as effective in this respect as IPPB in these studies in spite of the increase in $\dot{V}o_2$ is due to other adjustments that will be discussed later.

Results during O_2 breathing

Lung volume considerations. Since the subjects were switched to O_2 breathing at the end of a resting expiration, the functional residual capacity (L_T) measured here is that at rest. However, the 30-minute studies, in which the subjects were in a steady state of VH or IPPB before being switched to O_2 for measurement of L_T, show that the latter increases by less than 10% of its resting value during VH and IPPB at the pressure used here, 12 cm H_2O. Hence, interpretations based on the lung volumes in Table III are not substantially in error.

It is worthwhile to consider how a change in L_T during the study would affect the interpretation. If, in the present 15-minute studies, after the onset of VH or IPPB the fast spaces become more inflated and the volume of the slow space is unchanged, then this makes no difference to our interpretations with reference to distribution of ventilation and perfusion; these are largely independent of changes in these alveoli, which fully saturate their perfusing blood. If, however, L_3 increased at the onset of VH or IPPB by 10% above the values given in Table III, then the value derived for the ventilation of the slow space, $\dot{V}_{A3}$, would also be increased by 10%. This is so because the turnover rate, $\dot{V}_{A3}/L_3$ measured during the study is valid irrespective of these volume changes at the beginning of the study. In that case in a typical study the value derived for fractional perfusion of the slow space, $\dot{Q}_{C3}/\dot{Q}_T$, would increase from 0.57 to 0.59 and that for its ventilation-perfusion ratio, $\dot{V}_{A3}/\dot{Q}_{C3}$, from 0.266 to 0.283. These are small changes, and they show that in these subjects these derived figures are relatively insensitive to changes in lung volume during the study.

Although it is thought by some that the magnitude of the lung volume is related in some way to gas exchange, the physiological connection is not clear. Indeed, provided an alveolus is patent its effectiveness in gas exchange should be dependent on its $\dot{V}_A/\dot{Q}_C$ ratio and not on its volume. The large size of the slow space is not directly related to its blood gas exchange, though it is related to its slow N_2 washout, depending as this does on the turnover rate, i.e., the ventilation to lung volume ratio.

Turnover rates and their significance. In normal lungs there is a wide variation in ventilation per unit volume even among the less ventilated alveoli; hence the concept of the slow space does not fit the N_2 washout data very well. The frequency distribution of turnover rates somewhat resembles a bell-shaped normal frequency distribution curve. In emphysematous lungs, however, no normal or log normal frequency distribution will fit the data. The frequency distribution is very skewed in the sense that there is a high frequency of lung volume units with a very low turnover rate (22). This has also been shown by Gomez, Briscoe, and Cumming, treating total N_2 elimination in end tidal gas from both the lungs and the tissues in terms of a continuous distribution of turnover rates (29). Insofar as the washout into balloons of N_2 from the least ventilated parts of the emphysematous lung, after subtraction of N_2 eliminated by the tissues, behaves within the limits of experimental error like a single exponential function during prolonged studies, the concept of the slow space in this disease is a most realistic and useful simplification.

The turnover rates are the least derived and most certain measurements made in these washout curves. They are not in error whatever the degree of inflation of the lung. The turnover rate of the slow space increased during both IPPB and VH. The former had a much greater effect. This is in agreement with Torres and associates (12). The increase in this ratio was due to an increase in $\dot{V}_{A3}$ averaging about 35%. This increase in the ventilation of the slow space during IPPB is a small fraction (about one-tenth) of the total increase in alveolar ventilation. Evidently, most of the extra ventilation is wastefully directed to the fast spaces. This is the price that must be paid to increase by only about 0.4 L per minute the ventilation of the slow space, which constitutes most of the lung. Nevertheless, this small increase is of critical importance in blood gas exchange. The magnitude of the effect of IPPB in raising arterial O_2 saturation to normal can be explained by the fact that about 10% of the extra ventilation is directed to the slow space in our patients. In VH there is no comparable increase in the ventilation of the slow space as measured here. The rise in arterial oxygen saturation must be

attributed to other causes that will be discussed later.

Ventilation-perfusion ratios. The arterial blood in these patients with emphysema is a mixture of components that have been oxygenated to very different degrees in variously ventilated alveoli. In the simplified model used here the fast spaces have enough ventilation to fully saturate the perfusing blood, since even if the whole cardiac output perfused them their $\dot{V}_A/\dot{Q}c$ ratio would be more than unity. Arterial O_2 saturation in these patients is critically dependent on the quantity of the ventilation and perfusion of the slow space. Of these two, change in perfusion has the greater influence, since an increase has two deleterious effects: *1*) it lowers $\dot{V}_{A3}/\dot{Q}c_3$ and hence the O_2 saturation of blood oxygenated in the slow space; and *2*) it increases the quantity of unsaturated blood mixed into the arterial stream.

The method used to derive $\dot{V}_A/\dot{Q}c$ ratios and the distribution of perfusion is illustrated by considering a patient with a high arterial O_2 saturation and also a large and very poorly ventilated slow space. It is evident without calculation that there cannot be much blood perfusion of the slow space when the arterial oxygen saturation is high. When the quantitative relationship among the mixed venous O_2 saturation, the $\dot{V}_A/\dot{Q}c$ ratio in an alveolus, and the resulting end capillary O_2 saturation is taken into account, it is possible to determine an upper limit to the fractional perfusion and a lower limit to the $\dot{V}_A/\dot{Q}c$ ratio of the slow space. These limits are valid even if there are shunts, barriers to diffusion, and inhomogeneity of ventilation or perfusion within the slow space (22). They are in reasonable agreement with estimates of $\dot{V}_A/\dot{Q}c$ ratios by other methods employing radioactive krypton or dissolved urinary N_2 (30). The present study assigns numerical values to the ratio or its minimal value in the slow space that fit the data in each study. They lie in the range between 0.15 and 0.6 where small increases in $\dot{V}_{A3}/\dot{Q}c_3$ effect large increases in the O_2 saturation of the blood leaving these alveoli (28). The increase in the alveolar ventilation of the slow space observed in IPPB is by itself practically sufficient to account for the observed rise in arterial O_2 saturation. However, in VH, where

the rise in V_{A3} is less marked, the rise in arterial O_2 saturation is more than would be expected especially when the rise in oxygen consumption is taken into account. It is therefore necessary to invoke reduction of blood perfusion through the slow space as a contributing cause of the rise in saturation. Although the data indicate that this occurred, they do not define the underlying physiological mechanism.

Distribution of perfusion. The fractional perfusion of the slow space ($\dot{Q}c_3/\dot{Q}c_T$) fell in every patient during VH. The average was reduced by 40% from 0.55 to 0.34. Reduction in fractional perfusion in the slow space during VH is expected since some alveoli, included in the slow space at rest, apparently greatly increase their ventilation and become included among fast spaces. Their perfusion is no longer included in that of the slow space. During IPPB the data in Table III show that in one patient (J.F.) it did not change and in another (W.W.) it rose, whereas in the others it fell to a varying, usually small, degree. It therefore seems there was no consistent change in the fractional perfusion during IPPB.

The index of fractional perfusion in relation to fractional volume $[(\dot{Q}c_3/\dot{Q}c_T)/(L_3/L_T)]$ permits assessment of perfusion of the slow space when the number of lung units therein changes. It is an approximate measure of blood flow in an average anatomic unit in the slow space. The reduction of this index below unity quantitates the underperfusion of the slow space relative to its volume, which is seen even at rest in these subjects. During VH there was in these particular studies a reduced fractional perfusion per anatomic unit of slow space when the reduced volume of this space was taken into account.

The mechanism by which VH changes the distribution of perfusion in these studies is not known. It is possible that the different intrapleural pressure profile during VH improves the distribution of perfusion in a manner that cannot yet be defined. In this context it is of interest that other methods of changing the intrapleural pressure profile may sometimes have the same effect. Jameson, Ferrer, and Harvey (8) found that in one patient whose minute ventilation decreased in a tank respirator, there was a substantial increase in arterial oxygen saturation

and a decrease in Pa_{CO_2}. We have found, among patients studied in the Drinker respirator, several in whom ventilation decreased, distribution of ventilation did not improve, but in whom arterial oxygen saturation rose and arterial P_{CO_2} fell. In the absence of significant change in respiratory rate in these studies, the results were compatible with the notion that intrapleural pressure changes induced by the tank respirator had improved the distribution of perfusion.

Summary

Studies were made on 14 patients with chronic obstructive disease of the lungs at rest, during intermittent positive pressure breathing, and during voluntary hyperventilation. Changes in arterial blood gases measured during air breathing are correlated with changes in nitrogen washout curves measured during oxygen breathing.

Both intermittent positive pressure breathing and voluntary hyperventilation had the same effect on arterial blood gases, raising arterial oxygen saturation to a normal value and lowering arterial carbon dioxide tension to a subnormal value.

During both procedures there was an increase in oxygen consumption that was about four times as much per liter of added ventilation during voluntary hyperventilation as it was during intermittent positive pressure breathing.

During intermittent positive pressure breathing about one-tenth of the extra ventilation was directed into the slow space. This was enough to account for the observed rise in arterial oxygen saturation. During voluntary hyperventilation the increase in the ventilation of the slow space was less than one-tenth and was not enough to account for the rise in arterial oxygen saturation. This suggests that during voluntary hyperventilation the rise in arterial oxygen saturation was partly due to a reduced fractional perfusion of the slow space.

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