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CLINICAL AND PHYSIOLOGICAL STUDIES ON CHRONIC BRONCHITIS

IV. *Effect of Isoprenaline Aerosol on the* *"Alveolar Nitrogen Plateau"*¹

By

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INTRODUCTION

Uneven distribution of inspired gas in the lungs may be detected by recording the expired nitrogen concentration after or during oxygen inhalation. Two methods are commonly used. In the "washout test" consecutive breaths are recorded for several minutes. In the "single breath test" used in this study, a detailed recording is made of the exhalation immediately following one breath of oxygen (4, 8, 9, 14). The latter test is thought to reflect asynchronous emptying (or filling) of various parts of the lung, which is expected to be present in obstructive lung disease (24).

The present study is an attempt to get information about the effect of bronchodilatation on the equality of emptying. Studies were performed on normal and bronchitic subjects.

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MATERIAL

Thirteen healthy subjects, 6 male and 7 female, who were without significant cardio-pulmonary disease were studied. Mean age was 28 years (range 23-35). They were laboratory assistants, doctors, or medical students. Spirometric studies on 8 of the subjects showed $FEV_{1.0}$ between 80-115 per cent of predicted, and $FEV\%$ values of 71-95 per cent (Table 1).

The single breath N_2 test was performed on one or several occasions in all the bronchitics participating in the study (paper no. I), *i.e.* 30 males and 28 females (Table 1). Their spirometric data were reported in paper no. II.

Studies after inhalation of *isoprenaline* were performed on 10 healthy subjects and on 52 of the patients, 28 males and 24 females (Table 3). In 8 of the patients, who showed marked change in N_2 gradient, additional measurements were made of mean expiratory flows and airways dead space before and after *isoprenaline*.

PROCEDURE

The subjects were studied in the sitting position. The test was performed by the investigator or, in some cases, by another doctor. Care was taken to avoid that bronchoactive drugs had been taken before the tests. No subjects were studied earlier than 5-7 days after any endobronchial study.

After the control series of 4-5 curves, 3 deep inhalations of *isoprenaline* sulfate (0.18 mg) were made 10-20 seconds apart. One minute later the first in a new series of 4-5 single breath curves made three minutes apart, was obtained. In some subjects PEF measurements were made before and after the single breath curve series.

In 5 healthy subjects lung volume determinations were made before and after *isoprenaline* inhalation. N_2 curve series were obtained prior to the He curves before and after inhalation. Five minutes were allowed to elapse before the lung volume measurements started, thus preventing extra oxygen from remaining in the lungs (17).

TABLE I
*N₂ Gradients and FEV% in Groups of Bronchitics with Different Severity
of Airways Obstruction.*

Subj.	Parameters	Yr. 19—	Obs.	Yr. 19—	Obs.	Yr. 19—	Obs.	Normal N ₂ gra- dient 1st study	
								μ	+ 95 % conf. lim.
Group I: FEV% ≥ μ									
17	FEV% (max)	58	75			60	70		
	N ₂ (mean)	58	8.1	58	11.1	60	11.9	3.3	4.8
30	FEV%	60	76						
	N ₂	60	4.5	60	6.7			3.3	4.8
121	FEV%	58	79	60	74	61	74		
	N ₂	58	1.4	60	1.7	61	2.1	3.4	5.2
123	FEV%	58	84	60	82				
	N ₂	58	2.5	60	4.2			3.3	5.6
127	FEV%	60	83						
	N ₂	60	3.3					2.8	4.3
MV, I	FEV%		79		78		72		
	N ₂		4.0		5.9		7.0		
Group II: FEV% < μ ≥ μ-1 SD									
I	FEV%	59	79	62	77				
	N ₂	59	1.2	62	2.7			1.6	2.5
11	FEV%	59	66						
	N ₂	59	2.8					2.8	4.4
13	FEV%	60	68						
	N ₂	60	2.1					3.0	4.5
24	FEV%	58	65	60	48				
	N ₂	58	9.1	60	7.3			3.6	5.1
101	FEV%	59	79			62	83		
	N ₂	59	1.1	59	0.8	62	2.9	1.9	3.0
111	FEV%	59	78	61	71	62	75		
	N ₂	59	2.2	61	2.1	62	3.3	2.4	3.9
115	FEV%	59	76						
	N ₂	59	2.3					2.9	3.5
116	FEV%	60	77	61	79				
	N ₂	60	0.9	62	0.6			3.2	4.9
118	FEV%	58	76	61	74				
	N ₂	58	2.9	61	1.5			3.2	4.7
119	FEV%	61	73	62	84				
	N ₂	61	5.2	62	6.5			3.4	5.2

TABLE 1 (cont.)

Subj.	Parameters	Yr. 19—	Obs.	Yr. 19—	Obs.	Yr. 19—	Obs.	Normal N ₂ gra- dient 1st study	
								μ	+ 95 % conf. lim.
122	FEV% (max)	61	81						
	N ₂ (mean)	61	1.8					3.8	5.6
131	FEV%	60	75						
	N ₂	60	4.2					3.0	4.6
MV, II	FEV%		74		72		79		
	N ₂		3.0		3.1		3.1		

Group III: FEV% < $\mu-1$ SD $\geq$ $\mu-2$ SD

3	FEV%	59	64	62	78				
	N ₂	59	1.6	62	2.7			2.2	3.5
5	FEV%								
	N ₂	59	5.8	62	4.2			2.6	4.1
6	FEV%	58	61	60	45	61	46		
	N ₂	58	5.9	60	14.5	62	8.6	2.6	4.2
7	FEV%	59	66	62	60				
	N ₂	59	6.3	62	7.8			2.7	4.2
8	FEV%	59	60						
	N ₂	59	2.9					2.7	4.3
12	FEV%	60	64	62	67				
	N ₂	60	4.2	62	7.3			2.9	4.5
16	FEV%	59	59						
	N ₂	59	8.1					3.2	4.7
25	FEV%	60	49						
	N ₂	60	10.6					3.7	5.2
26	FEV%	60	59						
	N ₂	60	6.4					3.7	5.2
103	FEV%	59	75	63	69				
	N ₂	59	1.3	63	3.2			2.0	3.2
108	FEV%	62	76						
	N ₂	62	5.0					2.5	4.0
109	FEV%	59	71	60	81				
	N ₂	59	4.6	60	4.3			3.6	5.4
124	FEV%	60	69						
	N ₂	60	4.0					3.5	5.3
MV, III	FEV%		64		67		46		
	N ₂		5.1		6.3		8.6		

TABLE 1 (cont.)

Subj.	Parameters	Yr. 19—	Obs.	Yr. 19—	Obs.	Yr. 19—	Obs.	Normal N ₂ gra- dient 1st study	
								μ	+ 95 % conf. lim.
Group IV: FEV% < μ-2 SD									
2	FEV% (max)	59	53	62	60				
	N ₂ (mean)	59	3.6	62	5.3			2.1	3.5
4	FEV%	59	45						
	N ₂	59	6.8					2.2	3.5
9	FEV%	58	46	60	39				
	N ₂	58	6.9	60	5.9			2.7	4.3
10	FEV%	60	37	62	58				
	N ₂	60	5.2	62	2.5			2.8	4.4
14	FEV%	61	52						
	N ₂	61	9.7					3.2	4.7
15	FEV%	60	55	61	53	61	65		
	N ₂	60	2.0	61	6.8	62	4.0	3.3	4.8
18	FEV%	59	42						
	N ₂	59	6.2					3.4	4.8
19	FEV%	58	49	61	40	61	40		
	N ₂	58	9.1	61	13.1	61	11.6	3.3	4.9
20	FEV%	61	46						
	N ₂	61	16.4					3.6	5.1
21	FEV%	59	37						
	N ₂	59	4.2					3.6	5.1
22	FEV%	58	21	60	32				
	N ₂	58	11.0	60	10.2			3.6	5.1
23	FEV%	58	40	60	40				
	N ₂	58	6.1	60	6.1	62	5.4	3.6	5.1
27	FEV%	58	50	60	39	62	42		
	N ₂	58	5.9	60	6.5	62	5.5	3.6	5.1
28	FEV%	58	52	61	51	61	53		
	N ₂	58	7.7	61	6.2	62	6.6	3.7	5.2
29	FEV%	59	27						
	N ₂	59	11.5	59	7.0			2.6	4.2
102	FEV%	58	38	59	58	62	67		
	N ₂	58	5.1	59	3.7	62	4.8	2.0	3.2
104	FEV%	59	64						
	N ₂	59	3.2					2.0	3.3
105	FEV%	59	59	59	54				
	N ₂	59	8.4	59	7.3			2.0	3.3

TABLE 1 (cont.)

Subj.	Parameters	Yr. 19—	Obs.	Yr. 19—	Obs.	Yr. 19—	Obs.	Normal N ₂ gra- dient 1st study	
								μ	+ 95 % conf. lim.
106	FEV% (max)	59	70						
	N ₂ (mean)	59	4.0					2.0	3.4
107	FEV%	58	69	59	65				
	N ₂	58	5.0	59	3.8			2.0	3.4
110	FEV%	59	56	60	57	61	51		
	N ₂	59	4.1	60	6.6	61	6.9	2.3	3.9
112	FEV%	61	65	64	79				
	N ₂	61	4.9	64	4.5			2.5	4.1
113	FEV%	58	48	59	45	60	47		
	N ₂			59	3.8	60	6.3	2.4	4.0
114	FEV%	60	65	61	68				
	N ₂	60	2.7	61	2.8			2.7	4.2
117	FEV%	60	38						
	N ₂	60	8.4	60	7.4			3.3	5.0
120	FEV%	61	60						
	N ₂	61	2.3					3.5	5.3
130	FEV%	60	67						
	N ₂	60	3.5					2.1	3.4
135	FEV%	63	67						
	N ₂	63	6.7					2.4	3.9
MV, IV	FEV%		52		52		52		
	N ₂		6.3		6.1		6.4		

METHODS

The N₂ test was performed in a standardized manner, as described by *Kjellmer et al.* (17), using the same apparatus.

One litre of oxygen was inspired from, ideally, the resting expiratory level. The exhalation followed immediately and, according to instructions, with a relatively low and constant flow rate. Three minutes were allowed to elapse between each of usually five tests (17).

The respiratory gas was sampled from a needle-valve in a mouth-piece with an airmixer and with a dead space of 34 ml BTPS; the pressure drop at used expiratory flow rates was about 1 cm H₂O.

Nitrogen concentrations were measured with a Lilly nitrogen meter modified by *Lundin & Åkesson* (19). Nitrogen concentrations and expired volumes were simultaneously recorded on a direct writing ink jet recorder (Mingograf, Elema),

with an error of measurement of 2 per cent. There was an instrumental retardation, mainly due to gas-transport in the N_2 meter system, of in average 0.22 seconds measured at a 90 per cent deflection at a constant vacuum of 2.0 mm Hg.

Lung Volumes were obtained using the closed circuit helium method described in an earlier paper (29).

CALCULATIONS

Exhaled volumes of 750 and 1250 ml BTPS were signalled by the ink writer; after checking that the volume tracing was at zero at start of expiration, these signals were routinely used when measuring the nitrogen gradient between these two volumes. The time-lag was then added and the deflection on the corresponding point of the N_2 tracing was measured in mm. This value was expressed in per cent of the distance between the N_2 levels for oxygen and air, usually 50 mm, as calibrated before and after every series of curves. With a calibration chart the difference between the N_2 concentrations at expired volumes 750 and 1250 ml was then calculated; it was called the *N_2 gradient*. The mean of 4-5 tests were reported and compared to normal values for sex and age obtained on the same apparatus (25).

Airways or anatomical dead space (V_D) was calculated according to the method described by *Wilson et al.*, which was used in subjects with asynchronous emptying by the latter and by *Birath* (2, 21, 37). The inflection point of the S-shaped first part of the N_2 curve was used as representing the dividing point between dead space and "alveolar" gas. This is the point where the rate of change of N_2 concentration in the anatomic dead space passes from increasing to decreasing values. The distance corresponding to time-lag was added and the corresponding point on the volume curve was constructed. To obtain the volume of V_D the apparatus dead space of 34 ml has to be subtracted.

RESULTS

Nitrogen Gradients.

The nitrogen gradients in 10 healthy subjects were all within the normal range; *i.e.* below +95 per cent conf. limit (25).

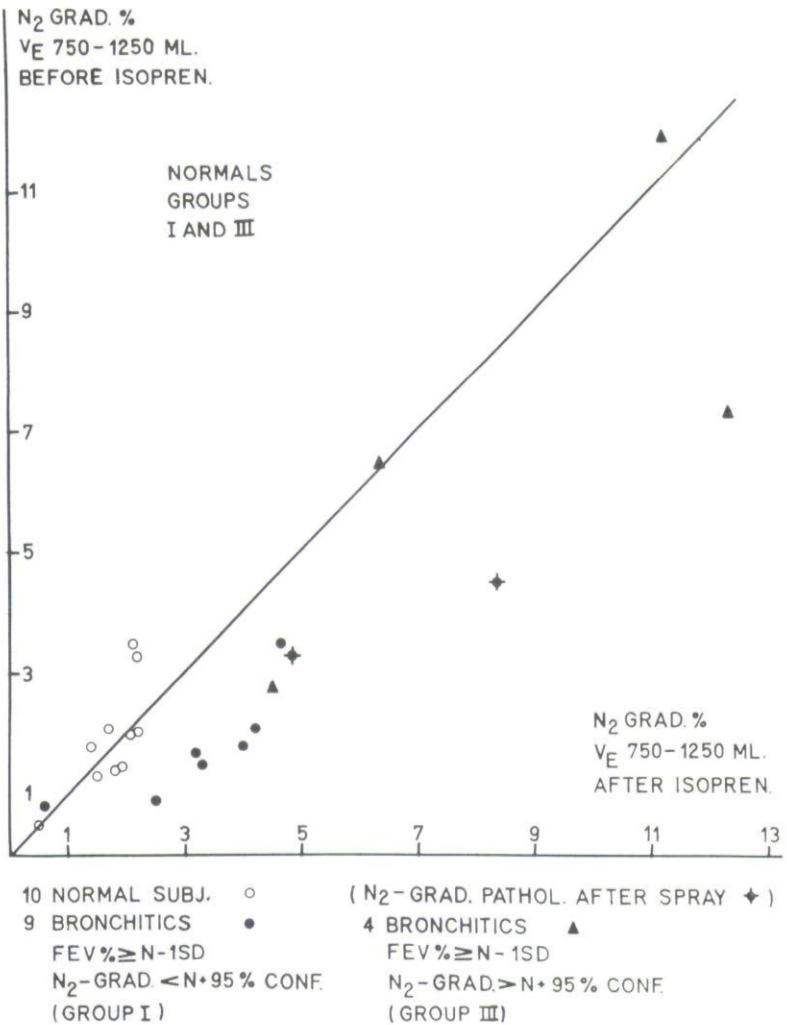


Fig. 1.

N_2 gradients before and after isoprenaline.

Normal subjects and bronchitics belonging to Groups I and III.

The individual N_2 gradient values and the $FEV\%$ figures obtained close to the N_2 test in the patient material are shown in Table 1. The classification here was made according to $FEV\%$ groups as in paper no. II.

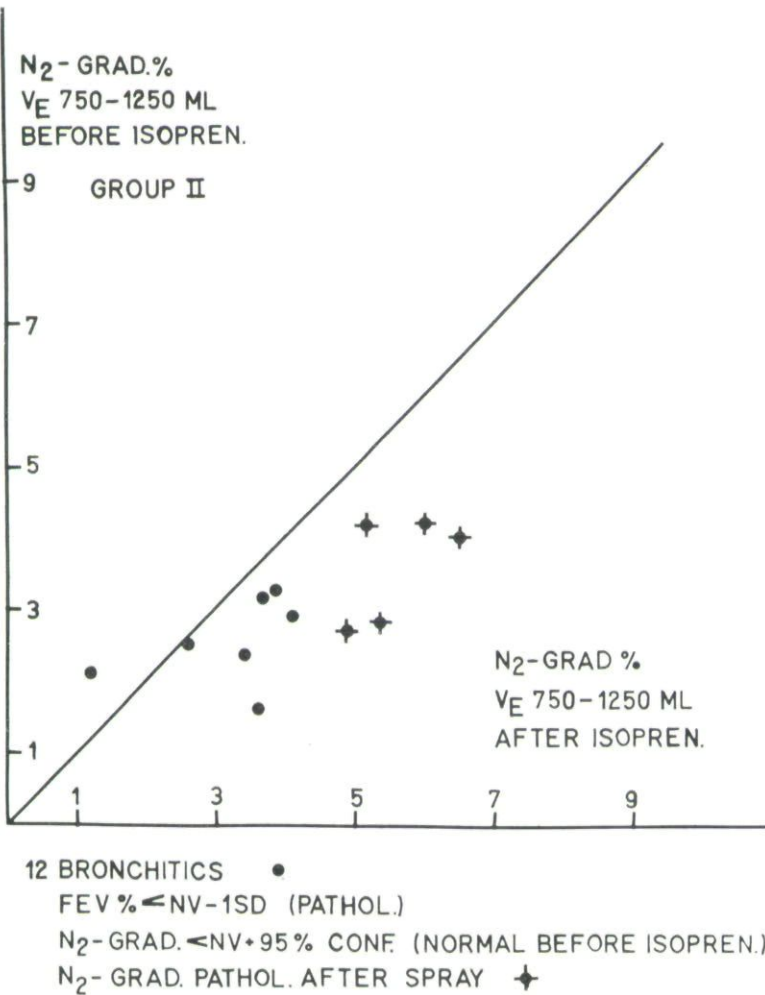


Fig. 2.

N_2 gradients before and after isoprenaline.
 Bronchitics in Group II.

In 36 patients N_2 test series were performed twice or more. In 8 patients the mean N_2 gradient varied between measurements made on different occasions; 7 changed from normal to pathological (Nos. 1, 12, 15, 30, 103, 113, 119).

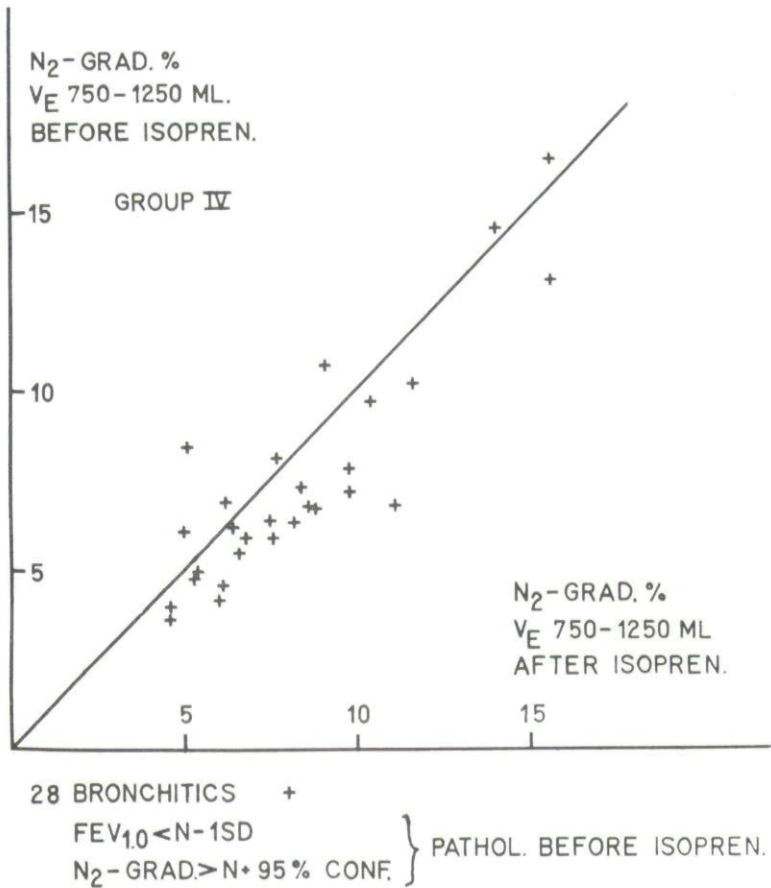


Fig. 3.

N_2 gradients before and after isoprenaline.
 Bronchitics in Group IV.

Among the 17 patients with an $FEV\%$ larger than predicted - 1 SD 6 had pathological mean N_2 gradients in one series of tests. In Group III 5/13 were abnormal compared to 24/28 in Group IV, a significantly higher frequency ($p < 0.01$).

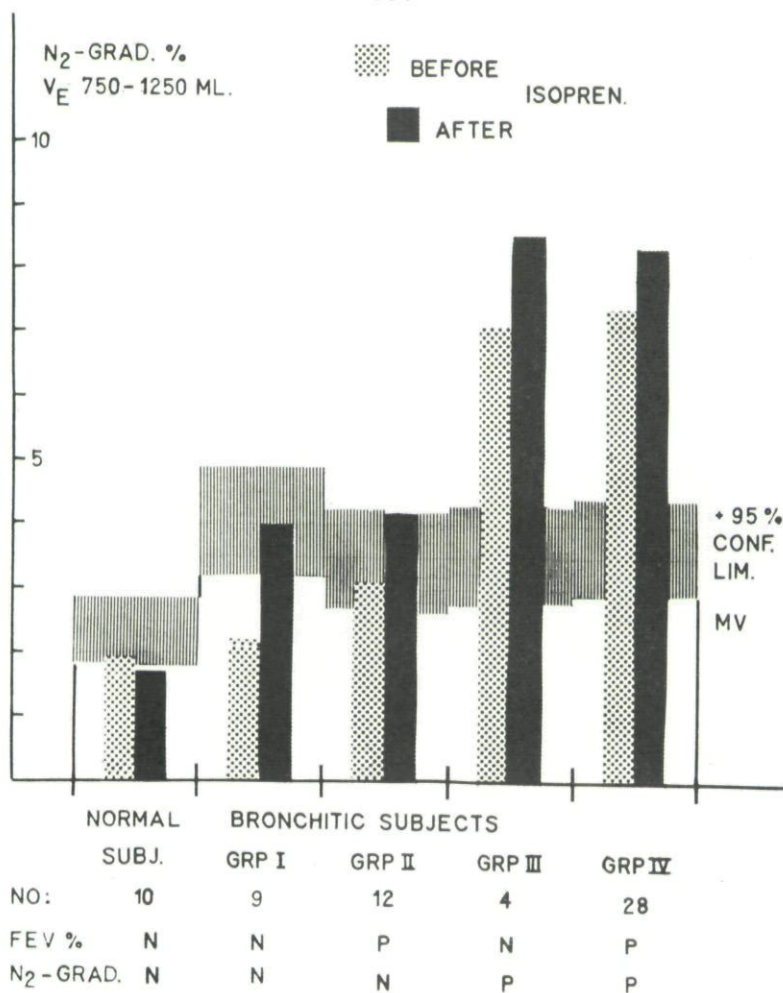


Fig. 4.

N_2 gradients before and after isoprenaline.

Total material, classification.

Effects of Isoprenaline Inhalation.

Before inhalation the average N_2 gradient in the *healthy* subjects was 1.9 per cent (range 0.5-3.5 per cent); the predicted value was 1.8 per cent. After inhaling 3 breaths of isoprenaline sulfate the mean gradient was 1.7 per cent (range

TABLE 2

Healthy Subjects. Effect of Isoprenaline on the Single Breath "Alveolar Nitrogen Plateau".

Subj.	Sex	Age	Spirometry		Predicted N ₂ gradient			Before and after isoprenaline			
			FEV _{1.0} % pred.	FEV % ₀	l ¹	+ 95% ₀ conf.		N ₂ grad.	N ₂ conc. at		FRC lit.
									750 ml	1250 ml	
GO	M	25	96	87	1.4	2.3	Before	1.4	50.6	52.0	3.65
							After	1.8	52.5	54.4	3.67
RS	M	23	110	95	1.3	2.1	Before	2.1	53.4	55.5	2.95
							After	1.7	50.8	52.7	2.98
EB	M	35	115	82	2.0	3.2	Before	1.4	54.7	56.1	3.41
							After	1.9	57.2	59.1	3.16
BS	M	30	111	79	1.7	2.8	Before	2.0	59.2	61.3	4.05
							After	2.1	57.9	60.0	3.38
PEL	M	27	—	—	1.6	2.5	Before	0.5	67.4	68.0	—
							After	0.5	69.4	69.8	—
UA	F	32	100	79	2.0	3.1	Before	3.5	50.5	54.0	—
							After	2.1	55.0	57.1	—
MLJ	F	27	—	—	1.9	2.9	Before	1.3	44.0	45.3	1.94
							After	1.5	48.6	50.1	1.98
MES	F	32	99	84	2.0	3.1	Before	1.8	57.2	58.9	—
							After	1.4	58.6	60.0	—
GP	F	25	88	71	1.9	2.9	Before	2.1	53.0	55.1	—
							After	2.2	54.1	56.3	—
AP	F	27	80	84	1.9	2.9	Before	2.9	39.4	42.4	—
							After	2.1	40.8	42.9	—
Mean:		28	100	83	1.8	2.8	Before	1.9	52.9	54.8	3.20
							After	1.7	54.5	56.2	3.03
Range: (23-35) (80-115) (71-95) (1.3-2.0) (2.1-3.2) (0.5-3.5) before (0.5-2.2) after											

0.5-2.2 per cent). The average N₂ per cent at 750 ml expired air (V_E 750) was 52.9 per cent before and 54.5 per cent after, corresponding values at V_E 1250 was 54.8 and 56.2 per cent. See Table 2, Figs. 1, 4.

The functional residual capacity obtained in 5 subjects before and after isoprenaline inhalation did not show any change (Table 2).

TABLE 3

*Effect of Isoprenaline on the "Alveolar Nitrogen Plateau",
Bronchitic Patients with Varying Degrees of Airways Obstruction and Asynchronous Ventilation.*

Subj.	Spirometry				Nitrogen test, peak flow								
	FEV _{1.0}		FEV _{0.5}		Pred.	Before isoprenaline				After isoprenaline			
	Obs.	0 ₁₀ pred.	Obs.	μ		-1SD	N ₂ % at		PEF	N ₂ % at		PEF	
							750 ml	1250 ml		750 ml	1250 ml		
Group I: Normal N ₂ gradient before Spray (≤ +95 per cent conf.) Normal FEV% (≥ μ-1 SD).													
Males:													
13	3.50	106	68	72	65	3.0 < 4.6	59.4	61.4	2.1	58.2	62.4	4.2	-
30	2.30	85	76	70	63	3.3 < 4.8	51.4	55.9	4.5	44.5	52.8	8.3	-
Females:													
101	2.91	91	79	85	79	1.9 < 3.0	55.2	49.9	0.8	52.6	53.7	0.6	-
116	2.40	96	77	78	73	3.2 < 4.9	58.3	59.2	0.9	57.1	59.6	2.5	-
118	1.68	76	74	78	73	3.2 < 4.8	48.2	49.7	1.5	34.2	44.5	47.8	3.3
121	2.19	100	74	77	72	3.6 < 5.4	47.7	49.5	1.7	-	54.9	58.1	3.2
122	2.48	110	81	76	71	3.7 < 5.5	47.5	49.3	1.8	-	40.6	44.6	4.0
123	2.48	124	87	76	71	3.9 < 6.8	50.3	54.5	3.5	-	47.4	56.1	4.7
127	2.19	89	83	79	74	2.8 < 4.3	44.7	49.8	3.3	-	42.4	48.2	4.8
MV	2.46	97	78	77	71	3.2 < 4.9	51.4	53.2	2.2 ^x	34.2	49.1	53.7	4.0 ^x
Group II: Normal N ₂ gradient before Spray. Pathological FEV% (< μ-1 SD).													
Males:													
3	3.35	92	64	78	71	2.2 < 3.6	57.9	60.6	2.7	57.2	62.3	4.9	-
8	2.75	82	60	74	67	2.7 < 4.2	58.7	61.7	2.9	56.3	60.5	4.1	-
10	1.74	54	37	73	66	2.9 < 4.4	57.3	59.9	2.5	55.7	58.4	2.6	452
15	2.16	77	58	70	63	3.3 < 4.7	52.9	56.9	4.0	48.5	54.9	6.5	348
11	3.52	110	66	73	66	2.8 < 4.4	57.2	60.1	2.8	55.9	61.2	5.3	-
21	1.43	46	37	69	62	3.5 < 5.0	55.4	59.6	4.2	55.8	60.9	5.1	-

TABLE 3 (cont.)

Spirometry					Nitrogen test, peak flow									
Subj.	FEV _{1.0}		FEV _{0.5}		Pred. $\mu \pm 95\%$	Before isoprenaline				After isoprenaline				
	Obs.	0.5 pred.	Obs.	μ		— 1SD	N ₂ % at		N ₂ grad.	PEF	N ₂ % at		PEF	
							750 ml	1250 ml			750 ml	1250 ml		
Females:														
103	2.63	86	75	83	78	2.0 < 3.3	52.4	55.5	3.2	428	52.5	57.5	3.9	436
104	1.53	57	64	83	77	2.0 < 3.3	60.2	63.5	3.2	—	53.8	57.6	3.7	—
111	2.22	101	71	80	75	2.4 < 3.9	49.9	52.0	2.1	—	48.8	51.9	1.2	—
114	2.38	93	65	79	74	2.8 < 4.2	42.6	54.6	2.8	—	46.4	49.9	3.6	—
120	1.58	66	60	77	72	3.4 < 5.2	55.1	57.4	2.3	—	51.5	54.9	3.4	—
131	1.89	80	71	79	73	2.9 < 4.6	51.1	55.3	4.2	—	53.2	59.1	6.0	—
MV	2.27	79	61	76	70	2.7 < 4.2	54.2	58.1	3.1 ^x	391	53.0	57.4	4.2 ^x	412
$x = p < 0.005.$														
Group III: Pathol. N ₂ gradient before Spray (> $\mu + 95$ per cent conf.) Normal FEV% ($\geq \mu - 1$ SD).														
Males:														
1	4.13	98	77	81	74	1.6 < 2.7	51.0	53.7	2.8	—	47.5	52.1	4.5	—
12	2.96	82	67	73	63	2.9 < 4.4	48.9	56.2	7.3	440	43.9	56.2	12.3	487
17	2.96	94	75	71	63	3.2 < 4.8	42.6	54.3	11.9	—	42.3	54.2	11.2	—
Females:														
119	1.91	89	73	77	72	3.4 < 5.2	41.5	48.0	6.5	292	44.6	51.0	6.3	310
MV	2.99	91	72	75	68	2.8 < 4.3	46.0	53.0	7.1	366	44.6	53.4	8.6	398

x = p < 0.005.

	5	1.73	54	54	74	67	2.5 < 4.1	48.7	52.8	4.2	370	47.1	53.1	6.0	450 ¹
6	6	1.50	43	45	75	68	2.6 < 4.2	40.6	55.1	14.5	—	40.5	54.9	14.0	—
7	7	2.16	66	66	75	69	2.8 < 4.4	41.7	49.4	7.8	267	44.3	54.0	9.7	315
9	9	1.55	45	39	74	67	2.8 < 4.4	47.9	54.5	5.9	—	47.5	55.2	7.6	—
14	14	1.53	50	52	72	65	3.2 < 4.7	46.0	55.7	9.7	—	46.6	57.1	10.4	—
15	15	1.99	77	53	70	63	3.3 < 4.7	53.7	60.5	6.8	—	46.3	57.4	11.1	—
16	16	2.50	88	59	71	64	3.2 < 4.7	49.0	57.1	8.1	—	49.1	56.9	7.7	—
19	19	0.95	32	45	70	62	3.5 < 5.0	38.3	51.4	13.1	—	33.4	49.1	15.6	—
20	20	1.30	42	46	68	61	3.6 < 5.1	41.2	57.7	16.4	—	43.2	60.4	15.6	—
22	22	0.61	20	37	69	62	3.3 < 4.8	54.1	64.4	10.2	—	50.4	62.0	11.6	—
23	23	1.07	36	40	70	63	3.4 < 4.9	47.6	53.7	6.1	—	46.5	51.5	5.0	—
24	24	1.28	45	48	69	62	3.4 < 4.9	51.3	58.6	7.3	—	45.8	55.4	9.7	—
25	25	1.02	38	49	68	60	3.7 < 5.2	51.9	62.4	10.7	—	56.5	65.5	9.1	—
26	26	1.95	66	59	68	60	3.7 < 5.2	44.9	51.3	6.4	—	44.7	52.1	7.5	—
27	27	1.22	41	42	68	61	3.8 < 5.3	52.4	57.9	5.5	186	52.8	59.4	6.6	221
28	28	0.97	37	53	68	61	3.7 < 5.1	51.8	58.0	6.2	—	52.9	58.9	6.4	—
102	102	2.60	85	66	83	78	2.0 < 3.3	46.2	51.0	4.8	—	44.7	50.2	5.4	—
105	105	1.96	70	59	82	77	2.0 < 3.3	53.8	61.0	7.3	—	47.6	56.0	8.4	—
106	106	2.14	73	70	82	77	2.0 < 3.4	55.4	59.2	4.0	—	54.4	59.1	4.6	—
108	108	2.02	72	73	80	75	2.4 < 4.0	46.6	51.7	5.1	—	45.5	50.9	5.4	—
109	109	1.99	81	71	81	76	2.2 < 3.7	37.4	42.1	4.6	—	39.0	45.1	6.1	—
110	110	1.19	47	56	80	75	2.4 < 3.9	35.3	42.1	6.9	—	38.8	44.9	6.2	—
112	112	1.71	68	65	79	74	2.6 < 4.2	47.8	52.7	4.9	—	49.6	56.4	6.8	—
113	113	1.22	47	47	80	75	2.9 < 5.1	48.5	54.8	6.3	—	44.3	52.5	8.2	—
117	117	0.92	38	38	78	73	3.3 < 5.0	47.4	55.8	8.4	—	47.7	52.8	5.1	—
135	135	2.14	78	67	80	75	2.4 < 3.9	50.5	57.2	6.7	—	43.2	49.7	8.8	—
MV		1.60	55	53	75	68	2.9 < 4.4	47.1	54.6	7.4	274	46.2	54.5	8.3	305

¹ When exhaling against resistance, mean N₂ gradient was 8.6 per cent.

TABLE 4

*Effect of Isoprenaline on the Single Breath
"Alveolar Nitrogen Plateau" in Bronchitic Subjects with Different Degree
of Airways Obstruction and Asynchronous Ventilation.*

Parameters mean value	N ₂ gradient and FEV ₀ groups			
	I	II	III	IV
	N ₂ grad. $\leq \mu + 95\%$ conf.		N ₂ grad. $> \mu + 95\%$ conf.	
	FEV ₀ %: $\geq \mu - 1SD$	$< \mu - 1SD$	FEV ₀ %: $\geq \mu - 1SD$	$< \mu - 1SD$
<i>1. Spirometry</i>				
FEV _{1,0} , lit.	2.46	2.27	2.99	1.60
Per cent of pred.	97	79	91	55
FEV%, recorded	78	61	72	53
Normal value (μ)	77	76	75	75
$\mu - 1$ SD	71	70	68	68
<i>2. N₂ Test, PEF</i>				
<i>A. Before Isoprenaline</i>				
N ₂ per cent at V _E 750 ml	51.4	54.2	46.0	47.1
N ₂ per cent at V _E 1250 ml	53.2	58.1	53.0	54.6
N ₂ gradient	2.2	3.1	7.1	7.4
Peak flow, lit./min.				274
<i>B. After Inhalation of 0.18 mg Isoprenaline</i>				
N ₂ per cent at V _E 750 ml	49.1	53.0	44.6	46.2
N ₂ per cent at V _E 1250 ml	53.7	57.4	53.4	54.5
N ₂ gradient	4.0	4.2	8.6	8.3
Peak flow, lit./min.				305
<i>Predicted Normal</i>				
N ₂ gradient	3.2	2.7	2.8	2.9
Upper normal limit ($\mu + 95\%$ conf. limit)	4.9	4.2	4.3	4.4
Number of subjects	9	11	4	29

In 52 patients the N₂ gradient was obtained before and after 3 inhalations of isoprenaline, Tables 3 and 4. The relations between normal and pathological pre-drug N₂ gradient and FEV% were used to form 4 groups, namely with

N₂ gradient lower than predicted +95 per cent conf.

- I: 9 patients with FEV% larger or equal to predicted – (normal).
1 SD (normal).
- II: 11 patients with FEV% less than predicted – 1 SD (pathol.).

N₂ gradient larger than predicted +95 conf. (pathol.).

- III: 4 patients with FEV% larger or equal to predicted – 1 SD.
- IV: 29 patients with FEV% less than predicted – 1 SD.

In Group I, both parameters being normal, average N₂ gradient was 2.2 per cent (range: 0.8–4.5) before isoprenaline and 4.0 per cent (range 0.6–8.3) after; the difference between pairs before and after was significant ($P < 0.005$), Table 4, Figs. 1, 4. The patients in Group II had a normal N₂ gradient but a pathological FEV%. The mean N₂ gradient increased on bronchodilation from 3.1 per cent (2.1–4.2) to 4.2 per cent (1.2–6.5), a significant increase ($P < 0.005$), Figs. 2, 4.

Group III contained 4 patients with a pathological N₂ gradient and a normal FEV%. The mean gradient, 7.1 per cent (2.8–11.9) changed, but not significantly, to an average of 8.6 per cent (4.5–12.3), Fig. 1. Patients in Group IV, in which both parameters were pathological, showed a similar but not statistically significant trend. Average N₂ gradient thus increased from 7.4 per cent (3.6–16.4) to 8.3 per cent (4.6–15.6), Table 4, Figs 3, 4.

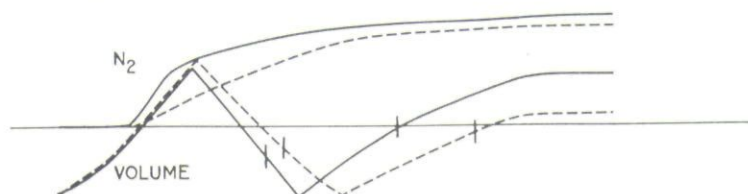
In all 4 groups the N₂ concentration at V_E 750 was lower after isoprenaline inhalation than before, while the N₂ concentrations at V_E 1250 was hardly affected.

Further Studies.

In 13 patients (Group I: 2 subjects, II: 3, III: 2, IV: 6), 4–5 peak expiratory flow measurements were made prior to

SUBJ. NO 12

N ₂ %	750 ML	1250 ML	GRADIENT
— BEFORE ISOPR	51.7	59.7	7.7 %
- - - AFTER	41.9	56.2	14.7 %



SUBJ. NO 15

N ₂ %	750 ML	1250 ML	GRADIENT
— BEFORE ISOPR	56	66	6.2 %
— AFTER	40.8	54.3	13.5 %

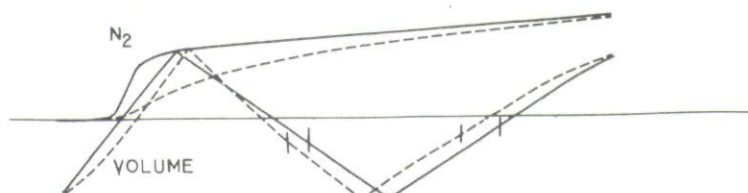


Fig. 5.

N₂ curves before and after isoprenaline in patients Nos. 12 and 15. Note the decrease in N₂ concentration at V_E 750 ml after isoprenaline. In patient No. 12 the expiratory flow is somewhat *faster* before, in patient No. 15 *slower* before than after drug. The zig-zag course of the volume tracing is due to changing phases in the rotational potentiometer.

the N₂ series before and after inhalation. The average value before was 321 lit. per min.; it increased to 351 lit./min., an average increase of 9 per cent ($P < 0.01$).

In 8 selected bronchitic patients, who showed a clear increase of the N₂ gradient after inhaling isoprenaline, the average N₂ gradient was 4.6 per cent before and 7.4 per cent after the drug; $P < 0.001$ Table 5, Fig. 5. The N₂ concentration at V_E 750 was 53.2 per cent before and 49.8 per cent after, ($P < 0.01$) while corresponding figures for V_E 1250 were 57.8 per cent and 57.3 per cent, respectively. Airways *dead*

TABLE 5

Effect of Bronchodilation on Airway Dead Space (V_D) and the "Alveolar Nitrogen Plateau".

Subj. no.	Group N ₂ FEV ₀ %	N ₂ gradient		Before and after isoprenaline						
					N ₂ grad 0/0	V _D ml	Exp. flow		N ₂ conc. at	
		Pred. μ	+ 95 ⁰ / ₀ conf.				0- 750 ml	750- 1250 ml	V _E 750	1250 ml
13	I	3.0 < 4.6	Before	2.1	164	35	48	59.4	61.4	
			After	4.2	203	49	55	58.2	62.4	
30	I	3.3 < 4.8	Before	4.5	122	72	39	51.4	55.9	
			After	8.3	158	45	24	44.5	52.8	
12	III	2.9 < 4.4	Before	7.3	208	36	34	48.9	56.2	
			After	12.3	233	36	30	43.9	56.2	
3	II	2.2 < 3.6	Before	2.7	148	39	36	57.9	60.6	
			After	4.9	164	51	65	57.2	62.3	
11	II	2.8 < 4.4	Before	3.1	251	44	41	57.5	60.6	
			After	4.6	258	47	42	56.9	61.5	
5	IV	3.3 < 4.7	Before	4.2	152	38	42	48.7	52.8	
			After	6.0	167	46	68	47.1	53.1	
<i>With expiratory resistance</i>			After	(8.6	203	50	85	44.6	53.2)	
15	IV	3.3 < 4.7	Before	6.8	105	35	22	53.7	60.5	
			After	11.1	139	25	15	46.3	57.4	
113	IV	2.9 < 5.1	Before	6.3	113	28	7	48.5	54.2	
			After	8.2	97	25	7	44.3	52.5	
Mean:			Before	4.6	158	41	34	53.2	57.8	
			After	7.4	177	41	38	49.8	57.3	
Sign. P				< 0.001	< 0.001			< 0.01		
<i>Decreasing N₂ gradient</i>										
117	IV	3.3 < 5.0	Before	7.4	120	51	24	46.5	53.8	
			After	3.9	159	71	45	50.8	54.7	

space increased from an average of 158 ml (105-251) to 177 ml (97-258), *i.e.* with 12 per cent ($P < 0.001$); this increase occurred in all subjects but No. 113. Mean expiratory flows for the volumes 0-750 ml and 750-1250 ml were found to be 41 and 34 lit./min. before and 41 and 38 lit./min. after the drug. The differences were not statistically significant.

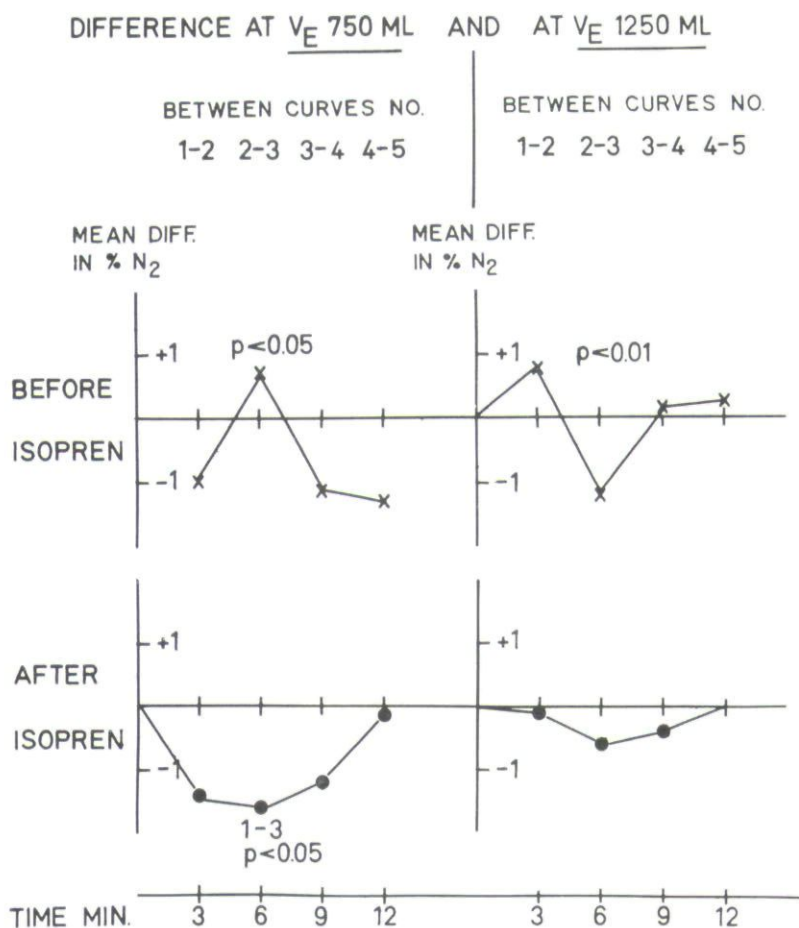


Fig. 6.

Differences in N_2 concentration between successive curves at V_E 750 and V_E 1250 ml before and after isoprenaline. Note the changing pattern before drug and the abolishment of the changes after isoprenaline.

In one patient, No. 117, there was a 3.5 per cent *decrease* in the N_2 gradient after isoprenaline; the same also occurred after intravenous theophyllamine, Table 5. Before drug inhalation expiratory flow rates during the N_2 test were 51 and 24 lit./min., for volumes 0-750 and 750-1250 ml, respectively; after inhalation definitely higher rates were obtained (71 and

45 lit./min., respectively). The airways dead space increased (120–159 ml).

In 6 bronchitics, relatively large *variations in flow rates* during the N_2 test were found on 16 different N_2 curves before spray. The maximal and minimal expiratory flow rates for the volumes 0–750 ml and 750–1250 ml were plotted with the N_2 gradients of the same curves. No significant correlation was found for N_2 gradient/mean expiratory flow rate (MEFR) 0–750 ml; there was a slight but significant negative correlation N_2 gradient/MEFR 750–1250 ml ($r = -0.58$, $P < 0.05$). Eighteen different curves on 6 subjects (5 from the group above) were also analyzed *after* bronchodilation. Significant negative correlations were obtained for N_2 gradient/MEFR 0–750 ml ($r = -0.62$, $P < 0.01$) and N_2 gradient/MEFR 750–1250 ml ($r = -0.65$, $P < 0.01$). Thus larger N_2 gradients were related to slower expiratory flow rates, especially after bronchodilation.

In order to analyze if some systematic changes occurred within the series, calculations of differences in N_2 concentrations between the 5 successive breaths at V_E 750 and at 1250 ml before as well as after isoprenaline, were made on 33 and 34 curves, respectively, of male bronchitics. The mean differences between pairs of N_2 concentrations in the successive curves can be seen in Fig. 6. At V_E 750 and 1250 ml there was a cyclic change before isoprenaline in N_2 concentration which became significant between curves Nos. 2 and 3 ($P < 0.05$). The pattern suggests a cyclic variation, which was abolished by isoprenaline inhalation (Fig. 6).

DISCUSSION

The single breath N_2 curve, after one breath of O_2 , consists of three parts, namely the early part of expiration of dead space gas containing no N_2 , a transient part with a steeply rising N_2 concentration, and a late part with usually a very gradual rise in N_2 concentration. The degree of this rise is expressed as the N_2 gradient. The gradual rise is thought to be

due to uneven and, especially, asynchronous ventilation (4). Two main concepts for this have been proposed:

Lung units with different time constants ventilate asynchronously (24). Regions with small time constants fill early and empty early; the reverse applies to regions with large time constants. This has been called the "first in—first out" concept (4).—On the other hand, there may occur late emptying of early filled parts, *e.g.* due to differences in filling sequences between right upper lobe and right lower lobe (18). Fowler similarly considered that uneven distribution of dead space gas to the early filling parts give rise to the N_2 slope in single breath curves by late emptying of these spaces, supporting the "first in—last out" concept (14). This seems to hold even in some patients with bullous lung changes, where downward N_2 slopes of the "alveolar plateau" have been recorded (30).

The time constant of any lung unit is the product of its compliance and resistance (24). If one unit has a larger time constant than another, this may be due to a raised compliance or a raised resistance; either of these two will thus make the unit "slower". If the slowness is due to increased compliance, the unit will be more ventilated than others; increased resistance, on the other hand, will cause relative hypoventilation.

In normal lungs the alveolar N_2 gradient has been reported *not* to change or to *increase* or *decrease* with increasing expiratory flow rates (12, 14, 17, 27, 38). Low flow rates were thought by Young to empty regions with low N_2 concentration, *i.e.* well-ventilated areas, while faster flows seemed to empty less ventilated regions with higher N_2 concentration. Based on these and other studies, the expiratory N_2 slope in the single breath test in normal lungs has been ascribed mainly to compliance differences in different lung units (12, 38).

In patients with airways obstruction unevenly elevated time constants occur. This is presumably due to regionally increased air flow resistance, and consequently a good correlation between pathological distribution and lowered FEV% has been reported (20, 33).

In the present study larger N_2 gradients were obtained in

patients during slower expirations; this has also been reported by earlier investigators (14, 27). These N_2 curve changes with flow rate indicate that changes in airways resistance rather than changes in compliance are the cause of the gradient (4, 12). The lower N_2 concentrations late in expiration at high flow rates in the present material may be due to closure or narrowing of poorly ventilated parts and even occurrence of "pendel luft" (24). Imposed expiratory flow resistance [in patient No. 5 and in other obstructive patients (3)], increases the N_2 gradient; this strenghtens the concept of expiratory airways narrowing as decreasing the contribution of gas from obstructed spaces. This expiratory obstruction may even include highly compliant areas without inspiratory flow obstruction. It seems as if the lung mechanical concept for the N_2 gradient by Otis *et al.* is supported in patients with generalized airways obstruction, as has also been suggested by Young (24, 38). Thus differences in compliceance may be the main reason for the N_2 gradients in normal subjects; in obstructive subjects it seems as if the airflow resistance is the most evident cause; in bullous areas stratification may contribute (4).

The effect of *inhaling isoprenaline in normal subjects* had a tendency to lower the N_2 gradient and to raise the N_2 concentration of the whole alveolar plateau. This is presumably due to a lowered resistance; the enlarged airways dead space obtained is compatible with some airway dilation (11, 26, 34, 35). The increase in N_2 concentration of the plateau also speaks for some increase in lung volume available for mixing with the inhaled litre of oxygen.

In the *patients, inhalation of isoprenaline* was followed by a definite lowering of N_2 concentrations at V_E 750 with only a small decrease at 1250 ml. This suggests distribution of a larger part of the inspired O_2 to the rapidly emptying regions, maybe also a volume reduction. The increase in airway dead space and in peak flow suggests a bronchodilation as the cause of this change in distribution. The bronchodilating drug was given by 3 inhalations starting from an expiratory position; it seems likely that the rapidly filling parts got a larger share of

aerosolized drug, becoming still more available for ventilation than the slowly inflating areas. This sequence of ventilation agrees with the "first-in—first-out" concept, unless there is also an uneven distribution of the reversibility of airways obstruction. Subject No. 117 serves as an example on the flow dependence of the N_2 gradient. After isoprenaline she showed a decrease of the N_2 gradient while the DS increased. In contrast to the other patients, her expiratory flow rate was almost doubled after bronchodilation. The lowered N_2 gradient may also depend on a more even bronchodilation causing a more synchronous emptying.

The N_2 gradient in patients is affected by different pre-inspiratory N_2 concentrations due to regional differences in ventilation/perfusion ratios. The effect of the respiratory quotient (R) may influence the N_2 slope also in cases with even ventilation but asynchronous emptying. A poorly ventilated space with better perfusion will show a high N_2 concentration; when such spaces empty late during expiration R decreases (4, 7). Slowly ventilated areas, however, are mostly found to be scantily perfused (5). The effect of parenteral bronchodilators, such as theophyllamine, is then probably also apt to be more pronounced in better perfused and better ventilated regions. Intravenous theophyllamine given to patients consequently evoked the same effect on the N_2 gradient as isoprenaline aerosol.

After inhalation of isoprenaline, regions with high ventilation/perfusion ratios ($\dot{V}_A/\dot{Q}$) may get more oxygen and the poorly ventilated parts even less than before. This may lead to a decline of arterial oxygen pressure due to an increased "physiological" shunt in parts unaffected by treatment with bronchodilators, as has been reported (15). It seems less likely that the isoprenaline lowers the ventilation-perfusion ratio in the well-ventilated and perfused alveols. The observed concomitant fall in arterial carbon dioxide tension may well be due to an increased ventilation of well-perfused alveols, which may be identical with early filling parts with a good bronchodilation.

Changes of tonus in peripheral, in contrast to central, airways may cause different effects on *lung volume and airways dead space* (V_D). V_D varies with lung volume and the caliber of especially the larger airways; an inverse relationship between resistance and airway dead space has been proposed (1, 11, 13, 16, 26, 28, 34, 36). Contraction of smooth muscles in the peripheral parts of the airways induces a decrease in dynamic and even in static pulmonary compliance, changing the volume and distensibility of the alveoli. The true nature of these changes is a regional increase in resistance to airflow in the periphery, with no change or even an *increase* of V_D (22).

After inhaling isoproterenol aerosol, airway dead space increases 20–40 per cent in normal subjects (34, 36).

A decrease of a previously increased lung volume by bronchodilation might lower the V_D but keep the airway resistance relatively unchanged due to the lowered total lung volume (6). An increase in TLC would increase V_D while flow resistance would fall relatively more. Söderholm found that after bronchodilation $FEV_{1.0}$ increased more than TLC in subjects where the N_2 gradient was also found to increase, which suggests that the flow resistance changed *more* than total lung capacity (32). This is in accordance with the report by Larson & Nadel that small changes in a low V_D were related to large changes in resistance (36). This may be the case with subject No. 113, whose N_2 gradient rose, while the V_D value decreased after marked bronchodilation. Tolou thought similar findings to be characteristic for peripheral obstruction (34). An increase in TLC some time after acute asthma attacks in children is not accompanied by an increase in pulmonary resistance (10). An increase in TLC, *e.g.* after inhalation of isoprenaline, would increase the expired mean N_2 concentration; the reverse would be true at a lowered total lung volume. In the present material, a lowering of the N_2 concentration was found after bronchodilation; no change or a decrease has been found after bronchoconstriction (31). The premises for evaluation of such a change in N_2 concentration are that the resting expiratory level and inspiratory volume are maintained

constant, and that the change is consequent over the nitrogen curve.

The washout of oxygen from a previous inspiration in normals takes less than 3 minutes (17). The slower washout in obstructive subjects may result in an increase in oxygen concentration in the lung, lowering the N_2 concentration in expired air. This mechanism seems not to explain the increased N_2 gradient after bronchodilation, since the effect would be to lower the N_2 concentration more in the most obstructive spaces which would decrease the gradient.

The significant fluctuations in N_2 concentrations revealed by the analysis of successive individual pairs of N_2 per cent at V_E 750 and 1250 ml before isoprenaline may be due to changes in airway muscle tone. The inhalation of oxygen might induce changes in smooth muscle tone. Cyclic changes in V_D occur in dogs ventilated with oxygen mixtures and other investigators have also found "airway peristalsis" (26, 35). The decrease of N_2 concentrations to a minimal value after isoprenaline may be interpreted as an abolishment of an active tonus, or a slowing of its phases. This interpretation is in accordance with the isoprenaline induced increase in airway dead space and lowering of airflow resistance in normal man (35).

The discriminatory power of the single breath test was probably heightened by the standardization of the inspiratory oxygen volume to 1 litre; which results in a higher mean N_2 concentration than after larger inspirations (17). The pulmonary volume over which the exhaled sample is studied is also lower than if the subject inhales maximally. Maximal inspiration decreases elevated airways resistance for some minutes, thereby probably influencing distribution (23). Accordingly, the N_2 slope was reported steeper when inspiratory volume was kept low (33). Slow breathing and a moderate inspiratory oxygen volume help to make the single breath test superior to spirometry in detecting small differences in flow resistance.

SUMMARY

I. Single breath nitrogen tests were performed in 10 healthy subjects and 58 bronchitic patients. With increasing degrees of airways obstruction the frequency of pathological N_2 gradients increased significantly.

II. After inhaling isoprenaline normal subjects showed an increase of the airway dead space but a possible decrease of the N_2 gradient.

In the bronchitics the N_2 gradient increased significantly after isoprenaline and most in the subjects who had no spirometric signs of airways obstruction. The N_2 concentration early during expiration was lowered; in the latter part of the expiration it was slightly lowered or unchanged. Airway dead space increased significantly in a selected group of patients with large increase of the N_2 gradient after isoprenaline and there was a significant increase in average peak flow values. These changes were judged to be due to bronchodilatation.

It is thought that "early filling spaces" were dilated most, creating a larger post-drug range of time constants. With slower expiratory flows there were significantly larger N_2 gradients, especially after bronchodilatation. This probably speaks for the "first-in—first-out" concept and for an increased airway resistance as the main cause of the N_2 slope during the single breath N_2 test in patients with bronchitis and airways obstruction.

It is thought that the single breath nitrogen test in the present modification is more apt to reveal slight regional differences in increased airflow resistance than dynamic spirometry. The detection of slight airflow obstruction may be further facilitated by inhalation of a bronchodilating drug like isoprenaline. By relating drug-induced changes in N_2 gradient and airway dead space, changes in conducting airways can be detected.

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