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THE PULMONARY CIRCULATION AND VENTILATION IN BRONCHIAL ASTHMA

By

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In connection with studies of cardio-pulmonary function during induced asthma (*Helander, Lindell, Söderholm & Westling*, 1962; *Helander, Lindholm, Lindell, Söderholm & Westling*, to be published) some observations on pulmonary circulation and ventilation were recorded in 34 male asthmatics when they were as free from symptoms as possible. Since these patients have been followed for up to five years after the investigation it was decided to compare the data obtained in the physiological studies with the clinical course of the disease in these patients.

CLINICAL MATERIAL

In selecting the patients the diagnosis of bronchial asthma was used as recommended by WHO in 1961, *i.e.* impaired breathing due to airway obstruction which varies either spontaneously or due to therapy. All patients were males hospitalized in the Department of Allergology.

To facilitate the study of a possible relationship between the clinical severity of the disease and the physiological data, the patients were divided into three groups. The most important clinical data are presented in Table 1.

Group I consists of ten patients. Their asthmatic attacks had been short and light with long free intervals. A specific allergy was detected in seven of them. Two of the patients had had a short period of treatment with corticosteroids and a third one had taken a small dose of corticosteroids for six months. The other seven had not had any steroid therapy. All the patients in this group managed their ordinary daily work both before and after the investigation during the period of follow-up.

TABLE I
Clinical Data

Group I										
<i>Patients with Slight Asthmatic Symptoms.</i>										
	A	B	C	D	E	F	G	H	I	J
Age	20	21	25	26	26	47	51	55	56	61
Heredity	0	2	1	0	1	0	1	1	0	1
Work	2	1	1	1	3	2	1	3	2	3
Duration	D	C	A	A	A	D	B	D	E	C
Steroid	0	0	0	0	0	0	0	2	1	1
X-ray	O	E	O	E	O	E	O	O	P	O
Eos.	0	0	0	0	0	0	1	0	0	3
Spec. allergy	D	D	D	D+H	D	O	D	O	O	E
Prognosis	A	A	A	A	A	B	A	A	B	B

Group II													
<i>Patients with Moderate Asthmatic Symptoms.</i>													
	A	B	C	D	E	F	G	H	I	J	K	L	M
Age	27	33	49	50	50	53	54	55	58	58	59	60	64
Heredity	2	0	0	0	0	0	0	0	0	2	0	0	0
Work	1	1	3	1	3	2	3	2	0	1	0	3	3
Duration	A	B	D	C	E	D	D	C	E	C	C	C	F
Steroid	3	0	1	1	3	4	1	4	3	1	2	0	0
X-ray	E	O	O	E	P	O	E	T	O	E	E	E	O
Eos.	0	0	1	3	1	1	3	0	1	1	0	0	0
Spec. allergy	O	O	O	O	O	O	O	O	O	O	O	O	O
Prognosis	B	B	D	M ¹	A	D	C	C	M ²	C	A	C	D

Group III											
<i>Patients with Severe Asthmatic Symptoms.</i>											
	A	B	C	D	E	F	G	H	I	J	K
Age	40	46	46	52	52	54	54	60	60	64	65
Heredity	1	1	1	0	1	0	0	1	1	0	1
Work	0	0	1	3	2	2	1	2	1	1	0
Duration	F	C	E	C	F	D	C	C	E	C	F
Steroid	3	3	3	2	3	3	4	1	2	4	3
X-ray	E	O	E	E	O	O	EP	T	E	O	O
Eos.	0	0	0	1	0	2	0	0	1	0	0
Spec. allergy	O	O	O	O	O	O	O	O	O	O	O
Prognosis	D	D	C	C	C	D	C	M ³	M ⁴	B	C

Explanations to Table 1.

Age is given at the day of investigation.

Heredity: 0 = no known relatives with allergic diseases.

1 = allergic disease known in parent, brothers or sisters or children.

2 = allergic disease known in uncles, aunts or first cousins.

Work: Conditions prior to hospitalization (or short time before).

0 = patient did not work for a considerable time or received pension.

1 = work conditions were not physically tiring (*e.g.* office work).

2 = moderately heavy manual labour.

3 = heavy manual labour.

Duration of asthmatic symptoms. The severity of the symptoms is graded group I, II and III and is not considered under duration.

A = symptoms continuously from childhood.

B = asthma during childhood, later free from symptoms, recurrence of symptoms during the five years prior to catheterization.

C = symptoms more than 10 years.

D = symptoms 5-10 years.

E = symptoms 2-5 years.

F = symptoms less than 2 years.

Steroids: 0 = has never received corticosteroids prior to function tests.

1 = received corticosteroids altogether not more than 3 months.

2 = received corticosteroids intermittently or continuously during 3 months to 1 year.

3 = received corticosteroids 1-3 years.

4 = received corticosteroids more than 3 years.

X-ray: Chest x-ray disclosed

O = a normal lung picture.

E = increased translucency.

T = inactive tbc.

P = small pleural adhesences.

Eos: Differential count of leucocytes showed.

0 = less than 500 eosinophiles/mm³.

1 = 500-799 eosinophiles/mm³.

2 = 800-1199 eosinophiles/mm³.

3 = more than 1200 eosinophiles/mm³.

Spec. allergy: Skin testing for allergens was done on all patients.

Allergens showing a positive skin reaction were given to the patient as an inhalation. Those who reacted positively on this provocation test were considered to have a specific allergy.

- O = no specific allergy.
- D = dust allergy.
- H = horse dander allergy.
- E = dust, horse and cow dander, barley and corn allergy.

Prognosis: All patients were followed 2-5 years after this investigation and the development of their disease carefully registered.

- A = gradual improvement.
- B = status quo.
- C = slight or moderate impairment.
- D = gross impairment.
- M = dead.

¹ Died 8 months later after operation for pulmonary abscess.

² Died 2 months later: status asthmaticus + spontaneous pneumothorax.

³ Died 3 months later in status asthmaticus.

⁴ Died 4 years later in status asthmaticus.

Group II consists of thirteen patients with moderate asthma. Their attacks were longer and more pronounced. All but three have been given steroid therapy; seven before the investigation and three after. All these patients had been away from their ordinary daily work for long periods of time due to asthma. In this group only one of the patients had improved after the investigation. In two patients the disease is unchanged, whereas in all the others it has progressed. Two patients have died.

Group III includes eleven patients with severe asthma. The attacks have been long and severe and have recurred with short intervals. All these patients have had continuous steroid therapy. None of them has been able to work in spite of the therapy. All patients except one have become progressively worse after the investigation. Two patients have died during the period of observation.

In all cases investigated, an exacerbation of the disease preceded the hospital stay. They all benefitted from symptomatic treatment which often included corticosteroids. When the benefit from further treatment was considered negligible and the patient's condition was deemed optimal all function tests were performed.

METHODS OF INVESTIGATION

Spirometry was performed with a modified Bernstein spirometer. The technique and normal values have been published elsewhere (*Grimby & Söderholm 1963*).

Physical fitness was judged from the performance on a bicycle ergometer. The heaviest work load which the patient could perform in a steady state was used as a measure of the patient's maximum capacity. The work load was increased in steps: 300, 600 and 900 kgm/min.

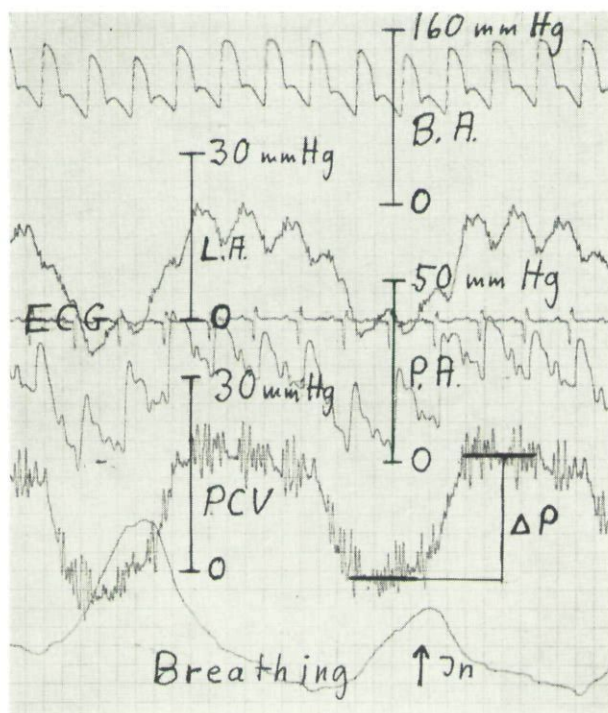


Fig. 1.

Records of pressures in the brachial artery (BA), left atrium (LA), pulmonary artery (PA) and PCV-position in a patient with bronchial asthma. Below is a pneumogram. ΔP = the amplitude of the respiratory pressure variations in the PCV-position.

Heart catheterization was performed in the morning after a light meal. A double lumen catheter (No. 9) was wedged in a pulmonary artery (PCV-position). Brachial arterial pressure was recorded from an indwelling polythene tube (Berneus, Carlsten, Holmgren & Seldinger 1964). Pressures were recorded with strain gauge manometers on a six channel direct writing recorder (Mingograph, Elema). A point 5 cm dorsal to the sternal angle was used as zero reference level. Mean pressures were measured by planimetric integration. Cardiac output was estimated according to Fick's direct principle. Gas analyses and measurements of oxygen saturation and oxygen capacity were performed as described by Söderholm (1957). Arterial carbon dioxide tension was measured as described by Berglund, Malmberg & Stenhagen (1964). Venous admixture to arterial blood (Q/Q) was calculated assuming a postcapillary saturation of 98 per cent (Söderholm & Widimsky 1962). The respiratory

TABLE 2
Spirometric Data and Capacity for physical Work.

		BSA m ²	VC	FEV%	MVV	Work cap.
Group I	A	1.60	3.15 (5.34)	89 (84)	96 (188)	300
	B	1.70	4.47 (4.94)	62 (84)	72 (180)	600
	C	1.86	4.91 (5.12)	66 (82)	145 (182)	600
	D	1.70	4.86 (4.57)	68 (82)	133 (172)	600
	E	1.95	5.89 (5.19)	76 (82)	203 (181)	900
	F	1.76	2.87 (4.68)	40 (74)	47 (146)	300
	G	1.85	2.95 (4.22)	32 (73)	31 (137)	600
	H	1.97	5.27 (4.71)	58 (71)	133 (134)	900
	I	2.06	3.46 (4.62)	51 (71)	83 (134)	600
	J	1.84	1.89 (4.23)	36 (69)	26 (126)	300
Group II	A	1.92	5.65 (5.87)	62 (81)	117 (178)	600
	B	1.70	4.83 (4.77)	71 (79)	134 (167)	900
	C	2.08	2.82 (4.36)	46 (74)	43 (140)	600
	D	1.77	3.70 (4.57)	56 (73)	78 (141)	600
	E	1.80	2.33 (4.51)	38 (73)	37 (142)	—
	F	1.90	4.90 (4.56)	59 (72)	123 (137)	600
	G	1.84	2.95 (4.02)	49 (72)	48 (133)	300
	H	1.89	5.61 (4.33)	48 (71)	93 (134)	—
	I	1.95	4.24 (4.36)	63 (70)	93 (129)	600
	J	2.12	4.03 (4.94)	36 (70)	31 (129)	300
	K	1.68	1.84 (4.00)	45 (70)	31 (141)	300
	L	1.74	4.68 (4.18)	69 (69)	114 (126)	600
	M	1.80	4.60 (4.56)	40 (67)	89 (118)	300
Group III	A	1.77	4.08 (5.11)	44 (76)	85 (156)	300
	B	1.82	2.90 (4.41)	38 (74)	41 (147)	600
	C	2.04	5.33 (5.22)	56 (75)	124 (150)	600
	D	1.72	3.70 (4.21)	44 (72)	60 (140)	600
	E	1.92	4.11 (4.75)	62 (72)	97 (137)	600
	F	1.81	4.42 (4.20)	67 (71)	108 (135)	900
	G	1.90	2.55 (4.39)	45 (72)	27 (138)	—
	H	1.56	2.30 (3.80)	27 (70)	25 (126)	300
	I	1.90	4.34 (4.61)	56 (69)	112 (126)	600
	J	1.92	3.36 (4.24)	45 (68)	39 (120)	600
	K	1.68	2.77 (3.97)	33 (68)	34 (121)	300

TABLE 2 (cont.)

Group I	n = 10	$\bar{X}$ 1.83 S. D. 0.14	3.97 (4.76) 1.28 (0.38)	57.8 (77.2) 18.3 (6.1)	96.9 (158) 56.6 (24.6)	570 221
Group II	n = 13	$\bar{X}$ 1.86 S. D. 0.14	4.01 (4.54) 1.22 (0.48)	52.5 (72.4) 11.7 (3.9)	79.3 (139.6) 23.7 (16.3)	518 194
Group III	n = 11	$\bar{X}$ 1.82 S. D. 0.13	3.62 (4.45) 0.93 (0.44)	47.0 (71.6) 12.2 (2.7)	68.4 (136.0) 37.6 (11.9)	540 190
All male subjects	34	$\bar{X}$ 1.84 S. D. 0.13	3.88 (4.58) 1.13 (0.45)	52.3 (73.5) 14.3 (4.9)	80.9 (144.0) 44.1 (18.7)	542 196

BSA = body surface area (m^2).

VC = vital capacity.

FEV% = forced expiratory volume
in one second in per cent
of vital capacity.

MVV = maximal voluntary

ventilation (L/min).

Work cap. = capacity for physical
work in steady state
(kgm/min).

(figures within brackets refer to predicted normal values).

pressure fluctuations in the PCV tracing (ΔP , Fig. 1) were used as an estimate of the intrapleural pressure variations (*Helander et al.* 1962). In one case left atrial pressure was recorded directly through a thin needle inserted from the jugular fossa. The puncture was performed by Dr. E. Linder, using the suprasternal technique.

RESULTS

Spirometric Investigation

The results of the spirometries are given in Table 2. The figures within brackets refer to the predicted values for a normal man of the same age, height and weight (*Grimby & Söderholm* 1963).

Although the mean age in group I was lower than in the other two groups there were no significant differences between the groups as regards spirometric performance. The vital capacity was lower than expected in all three groups. The ventilatory capacity was also reduced, judged from FEV% and MVV. The reduction in ventilatory capacity shows a tendency to increase from group I to group III but the differences were not statistically significant.

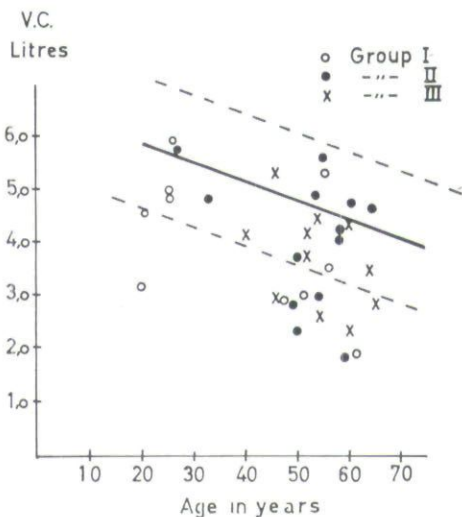


Fig. 2.

V. C. (vital capacity) in relation to age in male patients with bronchial asthma. The regression line ± 2 RSD was obtained from *Berglund et al.* (1963), who studied the normal variation. The patients were divided into three groups according to the clinical severity of the disease; group I being best.

The results of the measurements of vital capacity (V. C.) and of that part of the vital capacity which can be expired in the first second of a forced expiration (FEV%) are also given in Figs. 2 and 3, together with the regression line for the reduction in these parameters with age (*Berglund, Birath, Bjure, Grimby, Kjellmer, Sandqvist & Söderholm* 1963).

In these figures it may be seen that measurements of FEV% differentiate better between asthmatic subjects and normal subjects than do measurements of V. C. The scatter in the degree of deviation from calculated normal values was great in all three groups. In Fig. 3 it may be seen that among the patients in group I only three out of ten showed a FEV% that was within the normal limits. In group II, four out of thirteen and in group III, three out of eleven showed a normal value for FEV%.

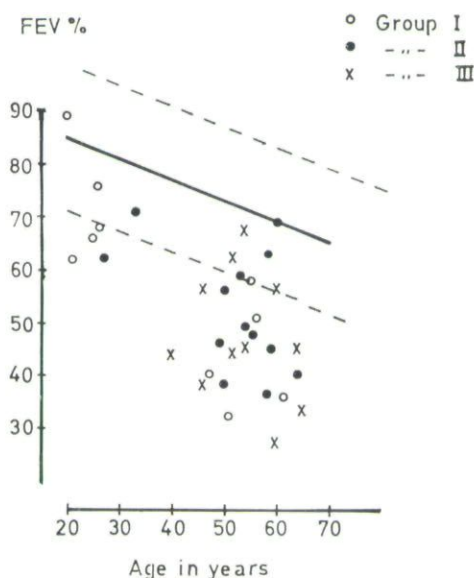


Fig. 3.

FEV% (the part of the vital capacity which can be expired in the first second of a forced expiration) in relation to age in male patients with bronchial asthma. The regression line ± 2 RSD for the normal variation was obtained from Berglund *et al.* (1963).

Bicycle Ergometry

The capacity for physical work, measured as the highest work load (300, 600 or 900 kgm/min.) that could be performed in a steady state as judged from heart and respiratory frequency is also given in Table 2. Again there was no significant difference between the groups although the mean age in the first group was lower. A comparison of group I and III shows that in both groups there were three patients who could perform only 300 kgm/min. Group I contains two subjects who could do 900 kgm/min and group III contains one such subject.

The Gas Exchange in the Lungs and the Central Circulation at Rest

The results of these studies are given in Tables 3 and 4.

TABLE 3
Respiratory Observations

		ΔP	f	$\dot{V}_E$	$\dot{V}_{O_2}$	R	S_{aO_2}	$Q_{sQ/t}$	P_{aCO_2}
Group I	A	5	14	7.6	228	0.78	97.4	2.6	36
	B	0	18	7.6	252	0.76	97.7	10.2	42
	C	7	21	10.7	243	0.85	88.1	29.2	40
	D	4	16	8.3	290	0.83	96.9	6.1	39
	E	6	8	5.0	274	0.62	97.4	2.8	30
	F	19	28	11.0	273	0.84	92.5	17.0	41
	G	10	14	8.2	269	0.81	95.4	8.9	41
	H	10	18	9.1	280	0.85	94.5	14.4	42
	I	14	14	7.1	208	0.86	96.1	6.5	39
	J	16	20	6.6	236	0.80	94.0	15.1	47
Group II	A	16	21	15.6	297	1.08	97.4	2.3	27
	B	5	22	9.2	280	0.82	96.2	7.3	52
	C	6	16	7.6	271	0.85	95.5	9.6	43
	D	5	18	7.4	274	0.78	95.5	11.5	45
	E	36	25	11.9	290	0.75	94.6	12.3	43
	F	5	12	7.5	268	0.82	94.9	16.7	48
	G	11	8	6.4	228	0.80	95.9	6.9	36
	H	10	28	6.7	241	0.77	96.2	6.5	39
	I	11	9	5.4	194	0.88	96.6	5.3	46
	J	9	22	8.9	308	0.84	94.1	12.6	53
	K	11	17	7.4	228	0.77	91.7	21.0	41
	L	7	12	7.7	265	0.80	97.2	4.1	37
	M	6	19	8.9	247	0.82	94.1	15.2	40
Group III	A	14	25	11.8	252	0.83	91.2	21.3	37
	B	35	18	10.0	322	0.76	90.6	24.7	50
	C	10	14	13.3	333	0.80	93.0	22.6	29
	D	24	16	10.2	282	0.82	90.6	24.0	41
	E	5	10	3.2	111	0.93	96.9	5.8	48
	F	10	25	8.5	279	0.80	91.9	24.7	39
	G	13	21	7.5	172	0.88	98.2	0.0	38
	H	8	9	5.8	192	0.77	92.6	17.0	46
	I	25	20	15.0	441	0.73	90.1	23.3	40
	J	18	17	8.4	271	0.81	94.1	13.0	33
	K	19	21	8.4	270	0.87	96.1	6.7	38

TABLE 3 (cont.)

Group I	n = 10	$\bar{x}$ 10.1	17.1	8.1	255.3	0.80	94.8	11.3	39.7
		S. D. 4.9	5.3	1.8	26.2	0.07	2.8	8.0	4.4
Group II	n = 13	$\bar{x}$ 10.6	17.6	8.5	260.8	0.83	95.4	10.1	42.3
		S. D. 8.3	6.1	2.7	32.0	0.08	1.5	5.4	7.0
Group III	n = 11	$\bar{x}$ 16.5	17.8	9.3	265.9	0.82	93.2	16.7	39.9
		S. D. 8.9	5.3	3.3	87.9	0.06	2.8	8.9	6.2
All male subjects	34	$\bar{x}$ 12.4	17.5	8.6	260.9	0.82	94.5	12.6	40.8
		S. D. 8.0	5.5	2.7	54.0	0.07	2.5	7.8	6.0

ΔP = respiratory pressure variations (see Fig. 3) (mm Hg).

f = respiratory frequency.

$\dot{V}_E$ = external ventilation (l per min.)

$\dot{V}_{O_2}$ = oxygen consumption (ml per min.)

R = respiratory quotient.

S_{aO_2} = arterial oxygen saturation.

Q_{s/Q_T} = venous admixture (% of cardiac output).

P_{aCO_2} = arterial CO_2 -tension (mm Hg).

Respiratory Pressure Variations in the PCV-Position (ΔP)

The highest value for ΔP that we have observed in eighteen healthy control subjects examined in the same way is 11 mm Hg. In the present study the number of patients who exceeded this value was in group I: three, in group II: two and in group III: seven. The range of variation within each group was, however, wide and there was no statistically significant difference between the groups.

Arterial Oxygen Saturation (S_{aO_2})

In this laboratory the lower limit of the normal variation of S_{aO_2} among healthy subjects has been found to be 94 per cent. In group I two patients, in group II one patients, in group III seven patients were below this limit. The scatter within each group was, however, large.

Venous to Arterial Shunt (Q_s/Q_t)

In eighteen healthy control subjects studied in the same way Q_s/Q_t varied between zero and 15 per cent. In each of group

TABLE 4
Hemodynamic Observations

		$\overline{PBA}$	$\overline{PCV}$	$\overline{PPA}$	SVR	PVR	$\dot{Q}$	$\overline{(a-v)}_{O_2}$	HR	SV
Group I	A	115	6	14	14.6	1.0	7.9	29	122	65
	B	127	10	16	21.2	1.0	6.0	42	76	79
	C	90	4	14	20.4	1.6	4.4	55	78	57
	D	108	2	8	11.6	0.6	9.4	31	108	87
	E	87	10	12	11.7	0.3	7.4	37	76	98
	F	100	12	19	20.0	1.5	5.0	54	120	42
	G	118	8	19	21.1	2.0	5.6	48	95	59
	H	124	8	11	17.0	0.4	7.3	38	93	78
	I	84	9	13	20.0	1.0	4.2	50	64	65
	J	122	6	22	22.8	3.0	5.4	44	92	58
Group II	A	121	7	13	19.2	1.0	6.3	47	100	63
	B	128	6	12	16.0	0.8	8.0	35	90	89
	C	109	11	15	17.7	0.7	6.2	44	68	90
	D	102	2	10	13.8	1.1	7.4	37	98	76
	E	92	3	20	14.6	2.7	6.3	46	114	55
	F	115	8	21	13.4	1.5	8.6	31	73	120
	G	113	3	13	27.8	2.5	4.1	56	88	46
	H	131	13	17	25.7	0.8	5.1	47	100	50
	I	189	11	20	51.1	2.4	3.7	52	68	54
	J	92	3	17	15.3	2.3	6.0	50	73	82
	K	110	8	24	18.3	2.7	6.0	38	80	75
	L	150	7	11	19.7	0.5	7.6	35	92	80
	M	146	7	21	21.2	2.0	6.9	36	60	73
Group III	A	139	3	15	27.8	2.4	5.0	50	103	49
	B	150	12	28	23.1	2.5	6.5	48	116	55
	C	103	5	13	11.4	0.9	9.0	37	130	69
	D	109	8	19	14.3	1.5	7.6	37	108	70
	E	131	5	13	43.7	2.7	3.0	37	70	43
	F	106	9	20	11.5	1.2	9.2	36	112	82
	G	118	2	12	35.0	3.0	3.4	51	106	32
	H	132	5	17	33.0	3.0	4.0	48	71	56
	I	114	5	15	21.5	1.9	5.3	47	110	50
	J	155	4	13	28.2	1.6	5.5	49	108	51
	K	105	9	16	17.5	1.2	6.0	45	100	60

TABLE 4 (cont.)

Group I	n = 10	$\bar{x}$ 107.5	7.5	14.8	18.0	1.2	6.3	42.8	92.4	68.8
		S. D. 16.2	3.0	4.2	4.1	0.8	1.7	9.1	19.6	16.6
Group II	n = 13	$\bar{x}$ 122.9	6.9	16.5	21.1	1.6	6.3	42.6	84.9	73.3
		S. D. 26.8	3.5	4.5	10.0	0.8	1.4	7.7	16.0	20.3
Group III	n = 11	$\bar{x}$ 123.8	6.1	16.5	24.3	2.0	5.9	44.1	103.1	56
		S. D. 18.7	3.0	4.6	10.4	0.8	2.1	6.0	17.9	13.8
All male subjects	34	$\bar{x}$ 118.7	6.8	16.0	21.2	1.6	6.2	43.1	93.0	66.4
		S. D. 22.8	3.2	4.4	8.9	0.8	1.7	7.5	18.8	18.4

$\bar{P}_{BA}$, $\bar{P}_{PCV}$ and $\bar{P}_{PA}$ = mean pressures in brachial artery, PCV-position and pulmonary artery (mm Hg).

SVR = systemic vascular resistance (in "units").

PVR = pulmonary vascular resistance (in "units").

$\dot{Q}$ = cardiac output (L per min.).

$(a-v) O_2$ = arterio-venous difference in oxygen content (ml per L).

HR = heart rate (beats per min.);

SV = stroke volume (ml).

I and II, three patients fell outside this range; in group III seven patients exceeded this range. Again there was a wide variation within each group and hence no statistically significant difference.

Cardiac Output ($\dot{Q}$ and Arterio-Venous Difference in Oxygen Content $(a-v) O_2$)

There were no statistically significant differences between the three groups as regards these parameters of circulatory function. In group I two patients had an $(a-v) O_2$ difference exceeding 50 ml/L blood, in group II there were also two values above 50 and in group III the highest arteriovenous oxygen difference was 51 ml/L.

Stroke Volume (S.V.)

The mean value for stroke volume was lower than normal in all three groups. The scatter was, however, wide within each group.

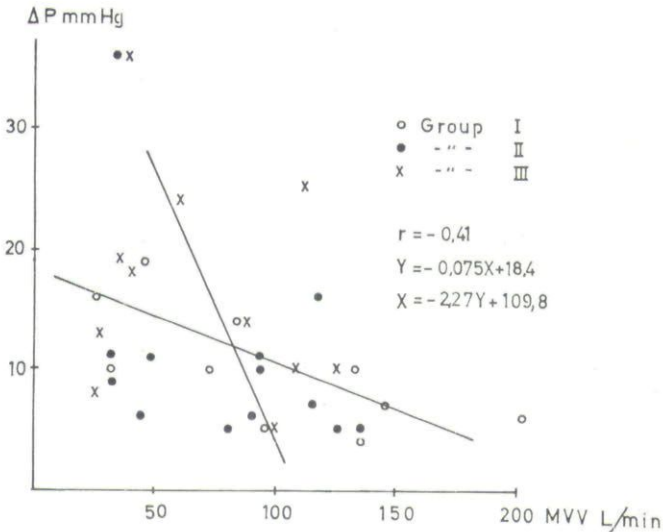


Fig. 4.

ΔP = respiratory pressure variations in the PCV-position in relation to maximal voluntary ventilation (MVV).

Mean Pressure in the Brachial Artery ($\bar{P}_{BA}$) and Systemic Vascular Resistance (SVR)

There was a tendency towards systemic hypertension in all three groups which was most pronounced in groups II and III consisting of the oldest patients. There was no statistical significance in the differences between the three groups as regards $\bar{P}_{BA}$ and SVR.

Filling Pressure for the Left Ventricle Measured as Mean Pressure in the PCV-Position ($\bar{P}_{PCV}$)

$\bar{P}_{PCV}$ exceeded the upper normal limit—12 mm Hg (Dexter & Rapaport 1958; Bjure, Helander, Lindell, Söderholm & Westling, to be published) in only one patient. The mean value for the groups decreased from group I to group III but the differences were not statistically significant.

Mean Pressure in the Pulmonary Artery ($\bar{P}_{PA}$) and Pulmonary Vascular Resistance (PVR)

$\bar{P}_{PA}$ exceeded 20 mm Hg in one patient from group I, in three patients from group II and in one patient from group III. There was no statistically significant difference between the three groups as regards $\bar{P}_{PA}$. Pulmonary vascular resistance, on the other hand, showed a clear tendency to increase from group I to group III and the difference between these groups was statistically significant ($P < 0.05$). Nevertheless, it should be noted that no patient had a pulmonary vascular resistance exceeding 3 units.

DISCUSSION

The reliability of some of the measurements and calculations will be discussed first.

The capacity for physical work was estimated on a bicycle ergometer, with the aid of which the work load could be increased in steps from 300 to 600, 900 and 1200 kg/min. The highest of these work loads which could be maintained in a steady state as regards pulse rate and breathing frequency was used as an estimate of the patient's maximal capacity for physical work. The method has the advantage of being simple, quick and the calculations are independent of the change in maximal pulse rate with age. The main disadvantage is that the method is crude. A similar method was used by *Irnell* (1964).

Cardiac output was measured according to Fick's principle which requires a respiratory steady state for a period long enough to collect an adequate volume of expired air. During these measurements this group of patients was in relatively good condition and there was no difficulty in collecting the expired air. The respiratory quotients showed little variation (Table 3).

Measurements of intravascular pressure in the pulmonary circulation usually presented only minor difficulties. However, in some patients, (Fig. 1) the intravascular pressures varied

widely with respiration. These respiratory pressure variations in the PCV-position were called ΔP and must be intimately related to the intrapulmonary pressure variations with respiration and hence with the work of breathing. These large pressure variations necessitated the use of planimetry to obtain mean pressures. It is now generally agreed that for most purposes the pressure recorded from the PCV-position can be used as a good estimate of the pressure in the left atrium. The influence of alveolar pressure on the pressure in the pulmonary capillaries has been much studied in recent years (*e.g.* Mead & Whittenberger 1964). It is stated that whenever alveolar pressure is higher than left atrial pressure, the blood flow through the pulmonary circulation will be determined by the pressure gradient between the pulmonary artery and the alveoli. This phenomenon has been referred to as the sluice mechanism or the vascular waterfall. Such a mechanism could easily come into play in the case of bronchial asthma where an increased alveolar pressure is necessary for the expiration. Fig. 1 gives us some opportunity to study this hypothesis. It shows the simultaneous record of pressure from the pulmonary artery, the PCV-position which is pre-capillary and the left atrium. It may be seen that the pressure in the PCV-position follows the pressure variations in the left atrium very closely. This suggests a free passage between the precapillaries and the left atrium in spite of the pronounced intrathoracic pressure variations. Furthermore, this record shows that the pressure variations with respiration in the pulmonary artery, the PCV-position and the left atrium run almost parallel. The respiratory pressure variations in these vessels were estimated to be: in the pulmonary artery 20, in the PCV-position 19, and in the left atrium 17 mm Hg. At the same time the mean pressure in these vessels was 21, 9 and 7 mm Hg respectively. A closer look at the records also shows that the pressure gradient from the pulmonary artery to the PCV-position or the left atrium increases during inspiration and decreases during expiration. The pulse amplitude in the pulmonary artery reaches its maximum at the end of the inspiration and

its minimum at the end of the expiration. The pulse amplitude in the brachial artery is maximal at the end of the expiration and minimal at the end of inspiration. These records thus suggest that the pressure in the PCV-position can be used as an estimate of left atrial pressure also in patients with increased intrathoracic pressure variations with respiration.

The resistance to flow in blood vessels is usually calculated using an analogy to Ohm's law for direct current. Thus the resistance in the pulmonary circulation equals the pressure difference between the pulmonary artery and the left atrium divided by the flow of blood. It is quite certain that the flow in the pulmonary blood vessels pulsates, not only with each heart beat but also with the breathing movements. Furthermore, it is also obvious that the pressure gradient changes with respiration. Thus the validity of this calculation of pulmonary vascular resistance may be seriously doubted. On the other hand, it does not at the present time seem possible to obtain a better estimate of the resistance to flow in the pulmonary vascular bed in man, and, as we shall see presently, the pulmonary vascular resistance calculated as above provided some meaningful information also in this material.

The results of the present investigation will now be discussed and compared with those obtained by *Irnell* (1964) in his extensive and thorough investigation of 116 cases of bronchial asthma from Uppsala. As might be expected, the most pronounced deviations from normality were found in the measurements of the ventilatory capacity. The maximal voluntary ventilation averaged 56 per cent of the predicted normal value. The corresponding figure in *Irnell's* material was 58 per cent. The present material seems to be best comparable with *Irnell's* groups B and C where he found little or no correlation between spirometric data and clinical grading. In our material this correlation was very weak, too. The patients in our group I had all been able to keep up their ordinary work, whereas in group III the patients were unable to manage their daily work. However, our measurements of capacity for physical work showed no significant difference

between group I and group III. In three patients who have died from bronchial asthma after the investigation the maximal voluntary ventilation averaged 77 L/min which is very close to the mean value for the whole group. In the same patients the capacity for physical work averaged 500 kgm/min which may be compared with 542 kgm/min for the whole material. Thus neither measurements of ventilatory capacity, nor estimates of capacity for physical work were of much use in judging the clinical course and prognosis of bronchial asthma. It seems much more likely that such measurements will be of value if they are carried out repeatedly in the course of the disease.

At first glance the hemodynamic observations are even more unimpressive. There was a slight systemic hypertension. The pulmonary vascular resistance did not exceed 3 units and was thus fairly normal. Five patients had an arterio-venous difference in oxygen content exceeding 50 ml/L. These patients were evenly divided among the three groups. The stroke volume tended to be low and in group III the average stroke volume differed significantly from the normal value given by *Granath, Jonsson & Strandell* (1964) for healthy old men. The stroke volume decreased significantly from group II to group III in our material.

Group III consisted of severely incapacitated patients who were unable to keep up their ordinary work in spite of treatment with corticosteroids. The bronchial asthma has progressed in all of them after the investigation and two of them have died from bronchial asthma. Yet the hemodynamics of the pulmonary circulation in these patients did not differ much from the normal. At the time of investigation there was no definite sign of pulmonary hypertension or cor pulmonale. These findings are in agreement with those of *Williams & Zohman* (1959) and *Irnell* (1964). They strongly suggest that bronchial asthma does not affect the pulmonary circulation to a clinically significant degree until very late in the disease, perhaps only in status asthmaticus. A similar conclusion may be drawn from the anatomical studies of *Gough*

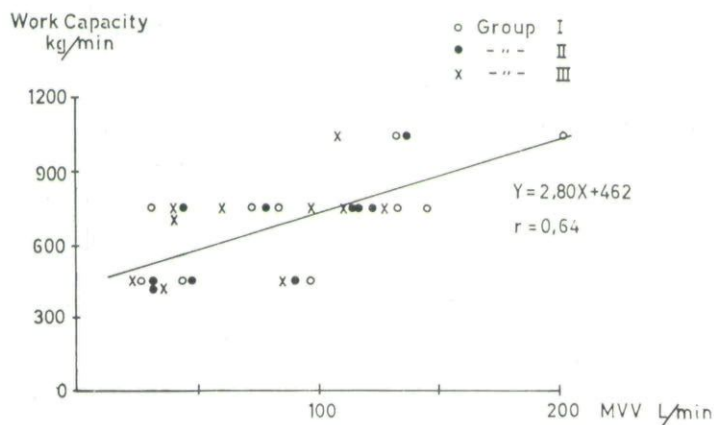


Fig. 5.

Capacity for physical work in relation to maximal voluntary ventilation (MVV).

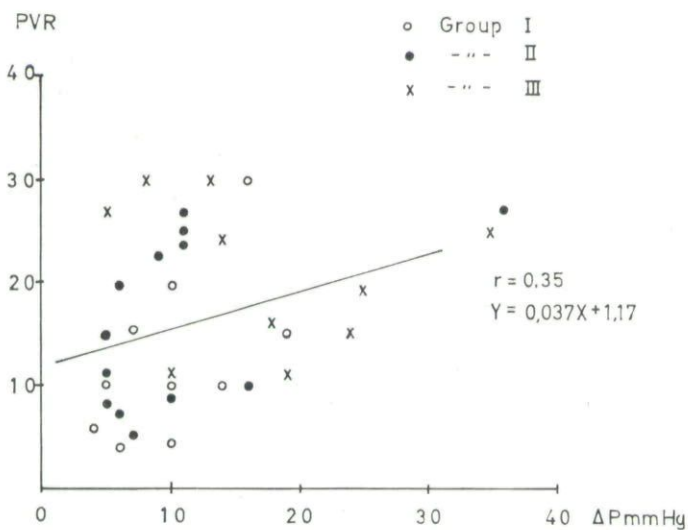


Fig. 6.

Pulmonary vascular resistance (PVR) in unit as related to respiratory pressure variations in the PCV-position (ΔP) in mm Hg.

(1961) who found little or no destructive emphysema in the lungs of subjects who had died from status asthmaticus. The right ventricle was normal in 19 out of 24 patients dying in status asthmaticus. Of those five who had signs of right ventricular hypertrophy two had also signs of destructive emphysema. Thus the results of physiological and anatomical studies seem to agree that there is little engagement of the pulmonary circulation in bronchial asthma.

A closer analysis of the present material does, however, reveal some points of interest. The work of breathing as judged from the respiratory pressure variations in the PCV-position was increased and especially so in group III. It seemed likely that the ventilatory capacity must be related to this increased work of breathing and as shown in Fig. 4, there was indeed a correlation between the ΔP and MVV in the material.

The correlation coefficient was -0.41 and the probability that this degree of correlation was of random nature is less than 1 per cent. Since bronchial asthma is primarily a pulmonary disease it seems reasonable to assume that the pulmonary function would be the limiting factor for the capacity to perform physical work. Fig. 5 shows that there was a positive correlation between maximum voluntary ventilation and the capacity for physical work.

The correlation coefficient was $+0.64$. A similar correlation has previously been found by *Dahlström* (1957) in patients with pulmonary tuberculosis and by *Irnell* (1964) in bronchial asthma. A graphical analysis (Fig. 6) of the relation between respiratory pressure variations in the PCV-position (ΔP) and pulmonary vascular resistance (PVR) indicated a correlation.

The correlation coefficient was found to be $+0.35$ ($P < 0.03$). This together with the fact that the pulmonary vascular resistance averaged 2.4 units in the three patients who died from bronchial asthma in our material, stimulated a new interest in PVR. It was found that there was a negative correlation between PVR and cardiac index, $r = -0.55$.

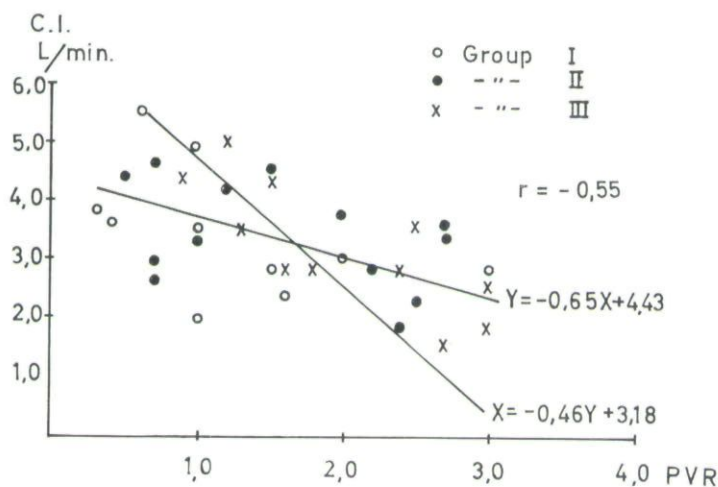


Fig. 7.

C.I. (cardiac index = cardiac output/body surface area) in relation to pulmonary vascular resistance (PVR).

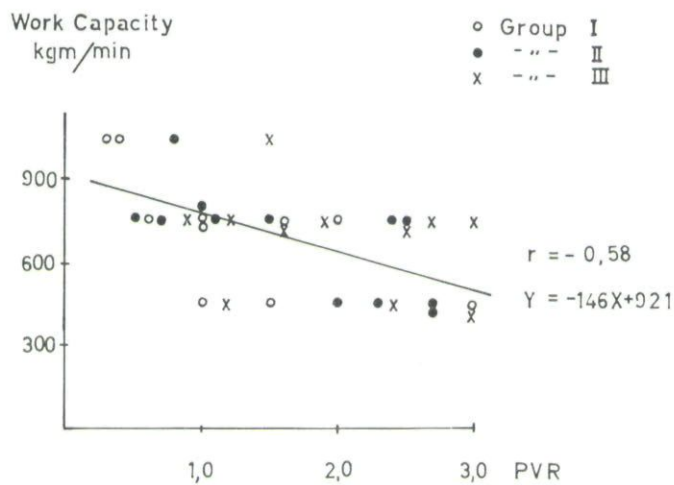


Fig. 8.

Capacity for physical work in relation to pulmonary vascular resistance (PVR).

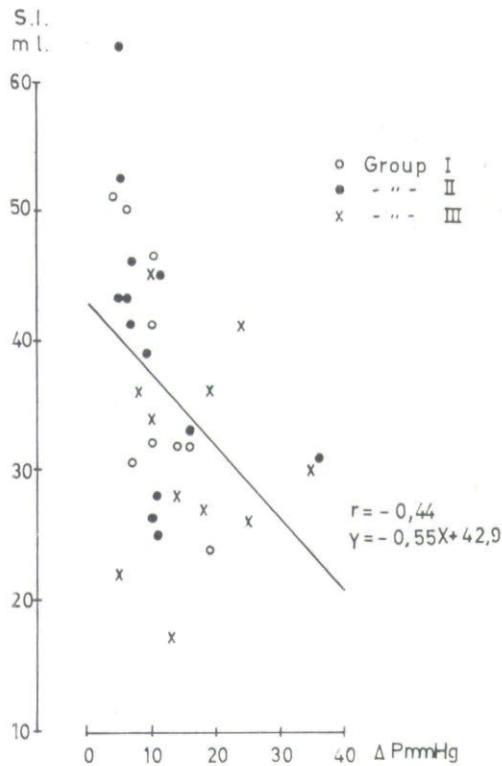


Fig. 9.

S. I. (stroke index = stroke volume/body surface area) in relation to respiratory pressure variations in the PCV-position (ΔP).

There was also a negative correlation between PVR and capacity for physical work, $r = -0.58$.

These observations attached more importance to measurements of pulmonary vascular resistance in these patients. It would seem that values for PVR exceeding 1.5 units, should be taken to indicate engagement of the pulmonary circulation. The highest value for PVR observed among healthy controls, aged 22–49 years, was 1.2 units. These control subjects were examined with the same technique and under the same conditions as the patients with bronchial asthma (*Bjure et al.*, to be published).

Our measurements of the respiratory pressure variations in the pulmonary circulation (Fig. 1) indicated that this pressure influenced both the systemic and the pulmonary circulation. Since the expiration in these patients required an increased alveolar pressure and since expiration was longer than inspiration it seemed likely that there would be some hindrance to the return of blood to the heart. Fig. 9 shows the relation between ΔP and the stroke index. The correlation coefficient was -0.44 ($P < 0.01$).

A similar analysis for the relation between ΔP and cardiac index revealed no such correlation indicating that the decreased stroke volume was at least to some extent compensated for by an increased pulse rate. It is perhaps not surprising that the hemodynamic effects of bronchial asthma with increased respiratory pressure variations in the thorax will to some extent resemble those of intermittent positive pressure breathing (*Werkö* 1947). The impedance to the return of blood to the heart caused by these increased respiratory pressure fluctuations might explain the tendency towards a low pressure in the PCV-position observed in the present series. A similar finding has been described by *Strandell* (1964) who in elderly men found the lowest PCV pressures in those cases where the highest airway resistance could be expected. It seems possible that decreased venous return and an impeded left ventricular filling might be factors contributing to death in fatal cases of status asthmaticus.

SUMMARY

The pulmonary circulation and ventilation was studied in 34 male subjects with bronchial asthma, at a time when they were as free from symptoms as possible. After these investigations the patients have been followed for a period of 4–5 years during which time three died from asthma. The patients were divided into three groups according to the clinical severity of the disease. There was little difference between these as regards most of the physiological measurements but the variation within each group was wide.

The work of breathing, as judged from the intrapulmonary pressure fluctuations, increased with the severity of the disease. The ventilatory capacity was reduced to about 60 per cent of predicted normal value.

The pulmonary vascular resistance was surprisingly normal but increased significantly with the severity of the disease, whereas the stroke volume decreased.

The correlation between various respiratory and circulatory functions was studied.

The influence of alveolar pressure on pulmonary vascular resistance is discussed.

ACKNOWLEDGMENTS

The study was supported by a grant from Svenska Nationalföreningen mot Hjärt- och Lungsjukdomar. The very valuable assistance given by Nurse *Anna-Greta Kindström* is gratefully acknowledged.

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